The Treatment of Peripheral Arterial Disease with Mechanical Compression and Angioplasty with Focus on Vascular Dysfunction

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Introduction

Peripheral arterial disease (PAD) shows a prevalence of 20-25% in the population over 65 years of age and encompasses two major clinical burdens: 1) limb ischemia and risk of amputation, and 2) systemic vascular dysfunction and involvement of other vascular beds that pertains cardiovascular complications, such as myocardial infarction and stroke which are the cause for death in 75% of PAD patients.

Due to limb or life threatening sequelae of PAD, optimizing treatment in terms of both minimal invasiveness as well as maximizing its effects is warranted.

The following summary encompasses original papers focusing on the treatment of PAD with intermittent pneumatic compression and surgical and endovascular infrainguinal revascularization with respect to local and systemic vascular dysfunction.

Intermittent Pneumatic Compression in Patients with Infrainguinal Bypass Grafting[1, 2]

Intermittent pneumatic compression (IPC) to the lower limb has been shown to augment native infrainguinal arterial inflow as well as skin perfusion in patients with non-critical limb ischemia. Furthermore, it has been reported that long-term IPC application improves absolute walking distance compared to best medical treatment alone. In patients with impaired wound healing due to limb ischemia and no further revascularization options, significant reduction in amputation rate through IPC has been demonstrated. Whereas the previous studies IPC was used in non-revascularized PAD patients, we investigated the immediate flow enhancing effects of IPC in limbs with infrainguinal bypass grafts.

IPC was delivered at maximum inflation and deflation pressures of 120 mm Hg and 0 mm Hg, respectively; inflation and deflation times of 4 and 16 seconds, respectively; and a proximal inflate delay of 1 second (foot/calf compression preceding that of calf/thigh). As assessed by ultrasound, its effect ranged from 50 per cent to 400 per cent lower limb arterial inflow augmentation compared to resting flow and its increase depended on localization of pressure application (foot, calf or thigh) and on vascular integrity (in comparison to healthy controls and arteriopaths without revascularization). Highest flow augmentation was found in healthy controls followed by grafted patients and was lowest in non-revascularized arteriopaths.

The results of these two studies have important clinical implications in grafted limbs when an increase in graft flow is required: a) Prevention of graft failures in low-output cardiac conditions, b) contraindication to anticoagulation, and c) during the peripheral vascular readjustment in late postoperative phase that often results in an increase in peripheral resistance. The paucity of conservative methods available for lower limb blood flow augmentation may allow IPC of the lower limb to emerge as a reliable, noninvasive therapeutic option, ameliorating claudication and assisting infrainguinal bypass graft flow. In

addition, IPC to the thigh adds to the armamentarium of currently known IPC options (foot or calf) promoting its applicability and efficacy.

Intermittent Pneumatic Compression and Local Vascular Dysfunction[3]

There are several physiological mechanisms through which IPC augments lower limb blood flow: a) increase in the arteriovenous pressure gradient, b) up regulation of endothelial nitric oxide synthases through intermittent shear stress augmentation and c) the transient abolishment of veno-arteriolar response (VAR). As veins empty, and for most deflation time (16s), venous pressure falls below 25mmHg. This then results in suspension of veno-arteriolar and myogenic reflexes, causing peripheral resistance to fall.

We investigated the relation between skin perfusion augmentation and integrity of local vascular function, the veno-arteriolar reflex (VAR). The effect of IPC on skin perfusion was assessed by means of laser Doppler flowmetry in control limbs and limbs of PAD. Laser Doppler flowmetry was used to measure VAR as percentage changes in skin blood flow in vertical position compared to horizontal and for skin blood flow measurement during the application of IPC to the foot, the calf, or both.

As expected, baseline VAR in controls was more pronounced with 63.8 % compared to PAD (31.7 %). IPC generated significantly higher skin blood flow in both groups than at rest, showing a higher percentage increase in controls (242 to 788 %) compared to PAD (98 to 275 %) depending on the site of compression delivery. There were significant correlations between VAR and the levels of skin blood flow augmentation for all three pressure modalities ($r=0.58$, $p=0.002$ for calf compression, $r=0.65$, $p<0.0001$ for foot compression and $r=0.64$, $p=0.0002$ for foot and calf compression).

These findings indicate that the integrity of postural lower limb veno-arteriolar response correlates with the level of skin blood flow augmentation induced by intermittent pneumatic compression suggesting that compression transiently suspends local autoregulatory vasoconstriction. Furthermore, the study support previous findings that VAR is impaired in non-critical limb ischemia.

Lower Extremity Angioplasty and Local Vascular Dysfunction[4]

Veno-arteriolar reflex is the local vascular auto-regulatory mechanism to adapt to postural changes and has been shown to be impaired or abolished in presence of limb ischemia as reported in the above summarized paper. We investigated the effect of lower limb angioplasty on VAR in patients with stable non-critical limb ischemia excluding diabetic patients.

Again, foot skin blood flow was assessed by laser Doppler flowmetry in the horizontal and sitting positions to determine VAR. VARs in healthy controls and in patients with mild to

moderate peripheral arterial disease before and after successful peripheral endovascular angioplasty of femoropopliteal lesions were assessed and compared.

In PAD, VAR was higher after angioplasty (55%) compared with VAR at baseline (33%). Although VAR increased after lower limb angioplasty, it remained lower than in healthy controls (68.4%). During the 6 months of follow-up, the ankle-brachial index and VAR remained unchanged in absence of restenosis, demonstrating a sustained effect on local vasomotor function.

The improvement in VAR following lower limb angioplasty indicates that VAR is sensitive to flow derangements. Given the results from the previous studies, demonstrating higher arterial inflow through IPC following revascularization (bypass grafting) and the fact that VAR integrity determines in part skin blood flow augmentation through IPC, it might be concluded that combination of angioplasty and IPC might have synergistic effects in treating patients with severe stages of PAD. Therefore, an improved VAR could result in greater effects of IPC on arterial and skin blood flow, suggesting a combined treatment of angioplasty and IPC.

Lower Extremity Angioplasty and Systemic Vascular Dysfunction[5]

Besides a local vascular dysfunction, systemic vascular dysfunction in PAD has been reported and shown to be predictive for cardiovascular prognosis. Intermittent claudication leads to impaired ambulatory activity and increase in oxidative stress due muscle ischemia, both known to deteriorate systemic vascular function, i.e. brachial flow-mediated dilation (FMD) as assessed by ultrasound. In a randomized, controlled study, we tested the hypothesis that endovascular lower limb revascularization ameliorates FMD and lowers inflammatory parameters.

Whereas FMD did not differ between treatment and control group at baseline, it significantly improved after revascularization in the angioplasty group (6.44 ± 2.88%; p=0.02). In contrast, FMD in the control group was 4.53 ± 3.17% (p=0.92) at 4 weeks of follow up. In the angioplasty group, there was a significant decrease in leukocyte count after angioplasty (from 7.6 ± 2.26 $x10^6$/ml to 6.89 ± 1.35 $x10^6$/ml, p= 0.03) whereas in the control group leukocyte count did not differ significantly compared to baseline (7.76 ± 2.64 $x10^6$/ml, p = 0.94).

This shows that lower limb revascularization might have beneficial effects beyond the sole relief of symptomatic claudication and that the abolishment of repeated muscle ischemia and/ or re-establishment of walking capacity could have beneficial effects in addition to best medical treatment. Yet it remains to be determined whether supervised walking exercise yields the same benefit as angioplasty, or rather a combination of angioplasty and supervised exercise training optimizes outcome.

The summarized papers report for the first time the extended use of application of IPC in grafted arteriopaths. In addition, novel insights into local and systemic vascular mechanisms in the treatment of peripheral arterial disease with intermittent pneumatic compression and angioplasty are described. These findings have implications in terms of both local and systemic sequelae of this disease. They offer rational for further investigations with combined treatment with angioplasty and intermittent pneumatic compression in the management of ischemic tissue lesions. Moreover, it may shift our understanding from lower limb angioplasty as a sole symptom relief therapy to effects that are beyond and might impact cardiovascular risk in PAD patients.

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Effects of intermittent pneumatic compression of the calf and thigh on arterial calf inflow: A study of normals, claudicants, and grafted arteriopaths

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Background. *Recent data indicate that intermittent pneumatic compression (IPC) of the foot may offer benefits in patients with intermittent claudication exceeding those of standard medications approved by the Food and Drug Administration. IPC of the foot (IPC_{foot}) and calf (IPC_{calf}) increases flow velocity in infrainguinal arterial bypass grafts and thus may prevent arterial thrombosis. Our aim was to evaluate the acute effects of IPC of the thigh (IPC_{thigh}), IPC_{calf}, and IPC of the thigh and calf ($IPC_{calf + thigh}$) in healthy controls, claudicants, and arteriopaths who have undergone infrainguinal bypass grafting for critical or subcritical limb ischemia.*

Methods. *Sixteen limbs of normals (group A), 17 limbs of claudicants (group B), and 16 limbs of arteriopaths (group C) who had undergone infrainguinal autologous revascularization were studied. Blood flow was measured in the limbs of normals and claudicants in the popliteal artery and in the grafts of revascularized limbs by using duplex ultrasonography. Mean velocity (mV), peak systolic velocity, end diastolic velocity (EDV), pulsatility index (PI), and volume flow (Q) were measured in the sitting position at rest and within 10 seconds from the delivery of IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$, IPC was delivered at maximum inflation and deflation pressures of 120 mm Hg and 0 mm Hg, respectively; inflation and deflation times of 4 and 16 seconds, respectively; and a proximal inflate delay of 1 second (calf compression preceding that of thigh).*

Results. *In all 3 groups with all IPC modes, the Q, mV, and EDV increased while PI decreased ($P < .05$). IPC_{thigh} was less effective than IPC_{calf}, but still increased Q (by 114%, 57%, and 59.8% in groups A, B, and C, respectively) and EDV, while decreasing PI in all 3 groups ($P < .05$). $IPC_{calf + thigh}$ was the most efficient mode, generating an increase in the median Q of 424% in controls, 229% in claudicants, and 317% in grafted arteriopaths. The addition of IPC_{thigh} to IPC_{calf} increased the mV and Q in group A ($P \leq .044$); the mV, Q, and EDV in group B ($P \leq .03$), and mV and PI by 24% and –27% in group C, respectively.*

Conclusions. *IPC applied to the thigh, either alone or in combination with IPC_{calf}, generates native arterial and infrainguinal autologous graft flow enhancement. The paucity of conservative methods available for lower limb blood flow augmentation may allow IPC of the lower limb to emerge as a reliable, noninvasive therapeutic option, ameliorating claudication and assisting infrainguinal bypass graft flow. IPC_{thigh} adds to the armamentarium of currently known IPC options (foot or calf) promoting its applicability and efficacy. (Surgery 2001;129:188-95.)*

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THE APPLICATION OF intermittent pneumatic compression (IPC) of the lower limb generates a significant increase in the native arterial calf inflow of patients with peripheral vascular disease.[1-3] The long-term application of IPC of the lower limb has been reported to enhance the walking ability of claudicants and improve the associated hemodynamic compromise.[4] The concept of improving

Table. Demographics of studied subjects and type of grafts

	Controls (group A)	*Claudicants (group B)*	*Grafts (group C)*	*Significance*
Limbs (right/left)	16 (7/9)	17 (12/5)	16 (9/7)	NS
Subjects (male/female)	10 (10/0)	15 (13/2)	16 (15/1)	NS
Age (range)	58 (34-75) years	64 (47-72) years	65 (44-77) years	NS
ABI (interquartile range)	> 1	0.68 (0.52-0.76)	> 1	< .0001 (A vs B)
Post-exercise ABI	> 1	0.31 (0.12-0.51)	> 0.95*	< .0001 (A vs B)
Time post-surgery	—	—	16 (5-39)	
Runoff artery	—	—	3 popliteal above knee†	
			5 popliteal below knee‡	
			2 anterior tibial§	
			6 posterior tibial§	

The ankle brachial indices *(ABI)* in claudicants are significantly lower than those of controls and grafted subjects ($P < .0001$).
*Those (8/16) who could complete.
†Procedures performed for short-distance claudication.
‡Procedures performed either for short-distance claudication (n = 2) or for critical limb ischemia (n = 3).
§Procedures performed for critical limb ischemia (4 ulcers).

the arterial compromise in peripheral vascular disease appeared first in the '30s,[5] but for decades failed clinical acceptability. Interest has resurged in recent years.[4,6]

In a recently conducted evaluation of its hemodynamic effects on the blood flow of infrainguinal arterial bypass grafts performed for critical or subcritical limb ischemia, IPC delivered to the foot (IPC_{foot}), to the calf (IPC_{calf}), or to both simultaneously ($IPC_{foot + calf}$), generated a volume flow enhancement ranging from 77% to 236%.[7] $IPC_{foot + calf}$ increased skin blood flux of the foot in claudicants[2] and grafted arteriopaths.[8] Potential short-term clinical applications of IPC include prevention of graft failure in the presence of attenuated arterial graft flow velocities[7] and enhancement of calf inflow and distal lower limb skin perfusion.[8]

The arterial leg inflow changes generated by IPC are predominantly caused by its action on the natural venous pumps of the lower extremities.[1,9-12] However, the effects of IPC applied to the venous pump of the thigh on lower limb arterial hemodynamics have never been evaluated. This study compares the immediate effects of IPC of the thigh (IPC_{thigh}), IPC_{calf}, and IPC applied simultaneously to the thigh and calf ($IPC_{calf + thigh}$) on native calf inflow in healthy volunteers and in claudicants and on the hemodynamics of patients who have had infrainguinal arterial bypass grafting performed for critical or subcritical ischemia.

MATERIALS AND METHODS

Study groups. The effects of IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$ on lower extremity arterial hemodynamics were evaluated in 16 limbs of control subjects (group A), 17 limbs with intermittent claudication (group B), and 16 limbs of arteriopaths with infrainguinal autologous bypass grafting (group C). The demographics of the subjects included in the study are depicted in the Table.

Selection of study subjects. Resting ankle brachial pressure indices were determined by dividing the higher ankle pressure (obtained from the dorsalis pedis or the posterior tibial arteries) by the higher of the 2 brachial artery pressures after a 15-minute resting period in the supine position. Post-exercise ankle-brachial pressure indices were also obtained after a 1-minute treadmill exercise test at a speed of 3.8 km/h and a gradient of 10%. Subjects with no history of arterial or venous disease, unremarkable clinical investigation, and lower limb arterial duplex scanning with resting and post-exercise indices exceeding 1.0 were included in group A. After Doppler pressures were determined, a graft surveillance examination was conducted with color flow duplex imaging (group C). Patients with successful (hemodynamically uncompromised) arterial grafting were recruited into the study. On duplex ultrasound evaluation, there was neither evidence of diameter stenosis greater than 30% in the entire length of the graft nor stenosis in the runoff circulation, with clean triphasic Doppler flow velocity waveforms demonstrated at the ankle. Group B consisted of patients with intermittent claudication due to superficial femoral artery occlusion, with ankle brachial pressure indices of less than 0.8 at rest, decreasing further post-exercise. Exclusion criteria for all 3 study groups were: congestive cardiac failure, peripheral edema, limb-threatening ischemia, clinically detectable diabetic neuropathy, lumbar sympathectomy, deep vein thrombosis, chronic venous insufficiency (CEAP 2-6[13,14] or venous reflux > 0.5

seconds), cellulitis or infected leg ulcers, and vasoactive medication (eg, nifedipine).

Examination and scanning protocol. Lower limb arterial blood flow was investigated with color flow duplex (HP Sonos 2500; Palo Alto, Calif) fitted with a 7.5/5.5 MHz linear array probe. In groups A and B, blood flow was evaluated in the middle third of the popliteal fossa (2 cm proximal to the medial condyle). In grafted arteriopaths (group C), flow was measured in the graft at knee level. Subjects in all groups were scanned in the sitting position, with their legs dependent, slightly extended at the knees and their feet resting on a low stool. The thigh and calf pads of the intermittent pneumatic compression system were gently applied and, after a resting period of 15 minutes to allow for flow stabilization, measurements were taken.

Resting arterial blood flow was initially measured (≥ 3 estimations). One of the 3 IPC modes (IPC_{thigh}, IPC_{calf}, or $IPC_{calf + thigh}$), chosen at random, was then applied and new flow measurements (≥ 3) obtained, starting from the second minute of pump action. Flow was always estimated immediately after and within 10 seconds of the delivery of IPC. After a 10-minute resting period, during which the pump was switched off, new resting flow estimations (≥ 3) were obtained. The next IPC mode, again chosen at random, was then applied and flow measurements (≥ 3) repeated, again starting from the second minute of pump action. The same protocol was followed for the evaluation of flow before and during the delivery of the third IPC mode.

The internal diameter of the arterial or graft lumen, the average of 3 to 4 estimations, was obtained by viewing the graft longitudinally and cross-sectionally on real-time B-mode and by using the tracker ball-guided calipers. Spectral analysis of pulsed Doppler signals insonating the entire lumen allowed determination of the mean velocity (mV). The gate of the sample volume was adjusted to the lumen of the vessel; and the 60-degree angle of insonation, and the site of gated Doppler sampling, carefully maintained. The mV is the time average of the mVs of each of the velocity spectra occurring during an interval of at least 4 cardiac cycles. The mV during a selected time, always within 5 seconds of the delivery of an impulse, was calculated by using software that enabled tracing of the waveform profiles. The reproducibility of this method has been previously evaluated.[3]

Volume flow was calculated from the mV multiplied by the cross-sectional area of the popliteal artery or graft and was expressed in mL/min. Data gained from automated computer-assisted analysis of the profiles of spectral flow velocity waveforms included the pulsatility index (PI), the peak systolic velocity (PSV) and end diastolic velocity (EDV). Pulsed Doppler spectral waveforms distorted by aliasing noise caused by venous flow or wall motion were discarded and measurements were repeated.

Analysis of data was performed with nonparametric statistics (Minitab 8.2 software package, Minitab Inc, State College, Pa; and StatView 4.57, Abacus Concepts, Inc, Berkley, Calif). Intragroup data were compared by using the Wilcoxon signed rank and Friedman tests; for intergroup statistics the Kruskal-Wallis test was used. Data are expressed as median and interquartile range.

Impulse unit. All 3 types of IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) were delivered by using a mechanical pneumatic pump (Art Assist 1000 unit; ACI, San Marcos, Calif). The pump consists of a pneumatic impulse generator and 2 inflatable plastic pads designed to fit the calf and thigh comfortably. The 2 large bore elastic tubes connecting the unit with each pad separately offer the versatility of isolating each pad from the other, thus allowing use of the 3 types of IPC. The investigation was conducted with the pump operating at the following presets: maximum inflation and minimum deflation pressures of 120 and 0 mm Hg, respectively; an inflation time of 4 seconds with a rise time of 0.3 seconds; and a rapid deflation time of 16 seconds. On application of $IPC_{calf + thigh}$, the onset of the calf impulse preceded that of the thigh by 1 second (delay time).

RESULTS

In all 3 groups, a significant increase in arterial calf inflow velocities and a decrease in the pulsatility index with all IPC modes (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) were documented. IPC_{thigh} generated significantly higher levels of volume flow than that at baseline. It was, however, less effective than IPC_{calf}. Concurrent application of IPC_{thigh} added significantly to the hemodynamic benefits generated with IPC_{calf}.

Mean flow velocity (mV). The mV increased on application of IPC_{thigh} in all study groups (Fig 1; $P < .001$). The percentage increases of the median mV were 95% in normals (group A), 51% in claudicants (group B), and 78% in grafted arteriopaths (group C). A higher median mV was generated with $IPC_{calf + thigh}$ (365% group A, 182% group B, 385% group C) than with IPC_{calf} (313% group A, 137% group B, 290% group C; $P = .044$ for group A; $P = .034$ for group B; $P = .5$ for group C). The mean velocity among claudicants was higher than that of the control and grafted subjects both at rest and with IPC ($P \leq .016$).

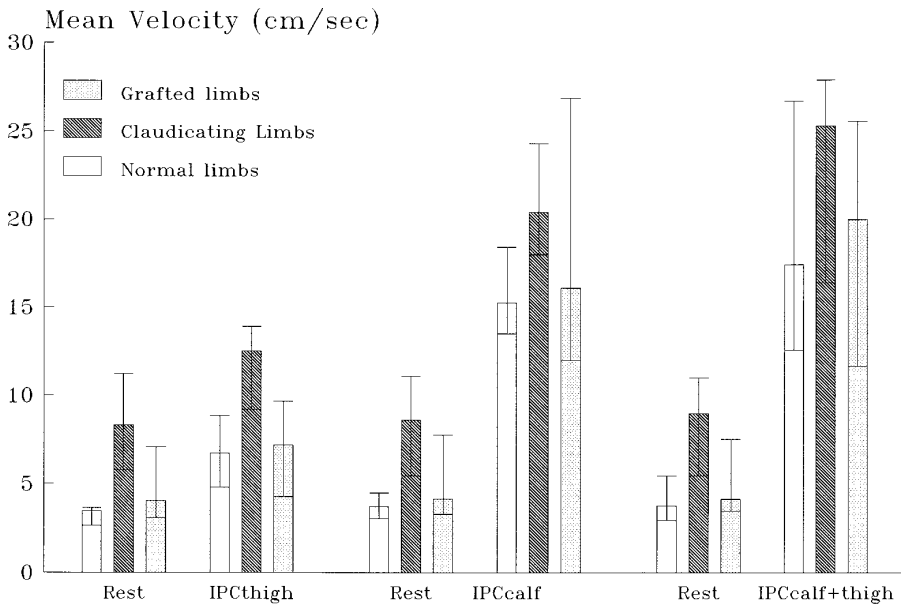

Fig 1. Effects of IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) on mean flow velocity (mV) in 16 limbs of healthy subjects, 17 limbs of claudicants, and 16 limbs with infrainguinal bypass grafting. In all groups, $IPC_{calf + thigh}$ and IPC_{calf} generated higher mV than IPC_{thigh} ($P < .001$), which produced a higher mV than that at rest ($P < .001$). There were no intergroup differences with $IPC_{calf + thigh}$, nor with IPC_{calf} ($P > .05$). IPC_{thigh} produced higher mV in claudicating limbs than in healthy or revascularized limbs ($P < .05$). (See Results.)

Diameter. No significant increase was documented in the diameter of the popliteal artery with IPC_{thigh}, IPC_{calf}, or $IPC_{calf + thigh}$ in groups A and B. There was a small but consistent increase in the graft diameter with $IPC_{calf + thigh}$ (from median 0.52 cm [interquartile range, 0.50-0.65 cm] to 0.54 cm [interquartile range, 0.50-0.66 cm] [$P = .016$]). The baseline popliteal artery diameter in claudicants (median, 0.34 cm; interquartile range, 0.28-0.41 cm) was much smaller than that in healthy limbs (median, 0.60 cm; interquartile range, 0.50-0.63 cm; $P = .001$). The baseline diameter of autologous grafts (median, 0.52 cm; interquartile range, 0.50-0.65 cm) was greater than that of the popliteal artery in group B ($P = .008$).

Volume flow (Q). Volume flow (Q) increased upon application of IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$ in groups A, B, and C (Fig 2, $P \leq .01$). $IPC_{calf + thigh}$ generated the highest median volume flow in all 3 groups. The percentage increase in the median Q with IPC_{thigh} was 114%, 57%, and 60% in groups A, B, and C, respectively; with IPC_{calf}, it was 347%, 122%, and 293% in groups A, B, and C, respectively; with $IPC_{calf + thigh}$, it was 424%, 229%, and 317% in groups A, B, and C, respectively. Although differences at rest were nonsignificant, the volume flow generated with IPC was higher among the controls and grafted arteriopaths than claudicants ($P = .0001$).

Peak systolic velocity (PSV). The peak systolic velocity (PSV) increased upon application of IPC_{thigh} ($P < .005$), IPC_{calf}, and $IPC_{calf + thigh}$ (in both, $P \leq .002$) in all 3 groups (Fig 3). There was no difference in the PSV produced by IPC_{calf} and by $IPC_{calf + thigh}$ in all study groups. The PSV in claudicants was significantly lower than that among control subjects and grafted arteriopaths both at rest and on IPC ($P \leq .005$).

End diastolic velocity (EDV). End diastolic velocity (EDV) increased on application of IPC_{thigh} ($P \leq .02$), IPC_{calf} and $IPC_{calf + thigh}$ (both $P \leq .001$) in all study groups (Fig 4). The EDVs with IPC_{calf} and $IPC_{calf + thigh}$ were higher than with IPC_{thigh} ($P \leq .01$). A higher median EDV was generated by $IPC_{calf + thigh}$ than with IPC_{calf} in all 3 groups; however, the difference was significant among claudicants ($P = .01$) only. The EDV among claudicants was higher than that in either control subjects or grafted arteriopaths both at rest and with IPC ($P \leq .01$).

Pulsatility index (PI). The pulsatility index (PI) decreased with IPC_{thigh} ($P < .03$), and IPC_{calf} and $IPC_{calf + thigh}$ (both $P \leq .001$) (Fig 5). In all groups, PIs with either IPC_{calf} or $IPC_{calf + thigh}$ were lower than with IPC_{thigh} ($P \leq .007$). There was no difference in the PIs generated by $IPC_{calf + thigh}$ and IPC_{calf}. The PI in group B, both at rest and with IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) was lower than

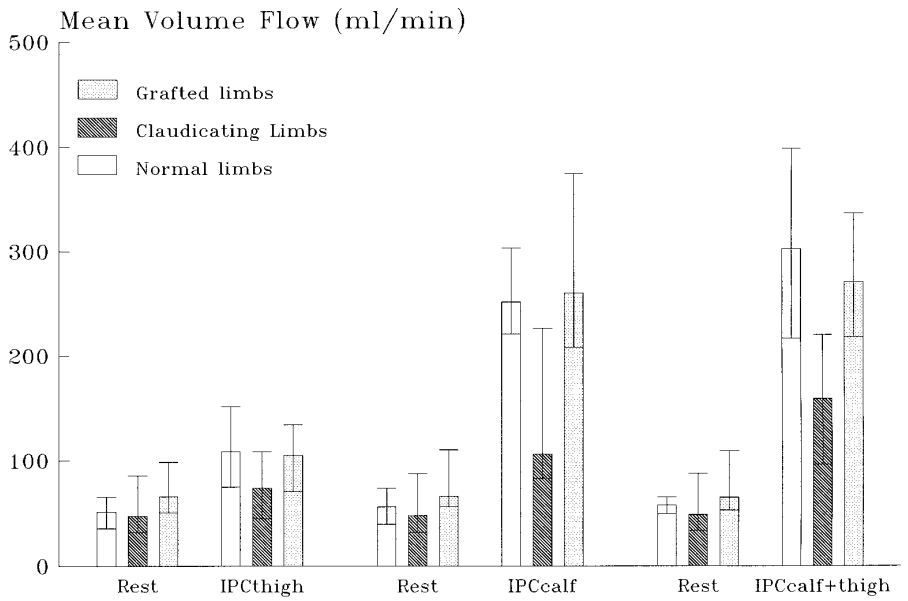

Fig 2. Effects of IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) on volume flow (Q) in 16 limbs of healthy subjects, in 17 limbs with claudication, and in 16 limbs with infrainguinal bypass grafting. $IPC_{calf + thigh}$, IPC_{calf}, and IPC_{thigh} increased Q in all groups ($P \leq .01$). $IPC_{calf + thigh}$ and IPC_{calf} produced higher Q than IPC_{thigh} ($P < .001$) in all study groups. There was no difference in the Q among the 3 study groups in the sitting position, at any one of the 3 resting time points ($P > .05$), or on application of IPC_{thigh} ($P > .1$). $IPC_{calf + thigh}$ and IPC_{calf} produced higher Q in controls and grafted limbs than in claudicating ones ($P < .01$). (See Results.)

that either in group A or group C ($P < .0001$). There was no difference in the PI with IPC between groups A and C upon IPC.

DISCUSSION

This study demonstrates that IPC applied to the thigh alone or in combination with IPC_{calf} is an effective means of enhancing the arterial calf inflow in limbs with unimpaired perfusion, intermittent claudication, and successful infrainguinal revascularization. IPC_{thigh} increased the median arterial calf inflow by 57% in limbs with claudication and the median graft flow in patients with femoropopliteal and femorodistal bypass grafting by 60%. Enhancement of the median popliteal volume flow was even greater in healthy limbs (114%). In all groups investigated, flow enhancement was associated with an increase in the EDV and a decrease in the PI. The changes in these indicators of peripheral resistance to flow[15] indicate that IPC of the thigh produces flow augmentation by attenuating resistance, as it does when applied to the foot, calf, or both simultaneously.[3,9]

The effect of IPC_{calf} on the arterial calf inflow was supplemented by the addition of IPC of the thigh ($IPC_{calf + thigh}$), which in all groups generated higher levels of volume flow than those produced by IPC_{calf} alone. Enhancement of popliteal artery volume flow with $IPC_{calf + thigh}$ (424%, 229%, and 317% in groups A, B, and C) was higher than that with IPC_{calf} (347%, 122%, and 293% in groups A, B, and C). The superiority of $IPC_{calf + thigh}$ in terms of flow enhancement was also evident in the PI, the median value of which was attenuated in all groups by another 20% to 34%, and the EDV, which increased among claudicants by 25%. It appears that the additional benefit to flow augmentation arising from the combination of IPC_{thigh} and IPC_{calf} is provided by further attenuation in peripheral resistance to flow.

Previous studies have demonstrated that $IPC_{foot + calf}$ can produce an increase in lower limb blood flow despite the presence of atherosclerosis.[1-3,9,10,12] The current study differs in that it shows for the first time that IPC_{thigh} is an alternative method of generating arterial calf inflow enhancement in claudicants and patients with infrainguinal arterial grafts. It also shows that IPC_{thigh} can be combined with IPC_{calf}, promoting its beneficial effect on peripheral flow.

There are 3 mechanisms by which IPC of the lower limb enhances arterial calf inflow. The first is the only one to have been proven: IPC expels venous blood from the leg into the thigh, reducing

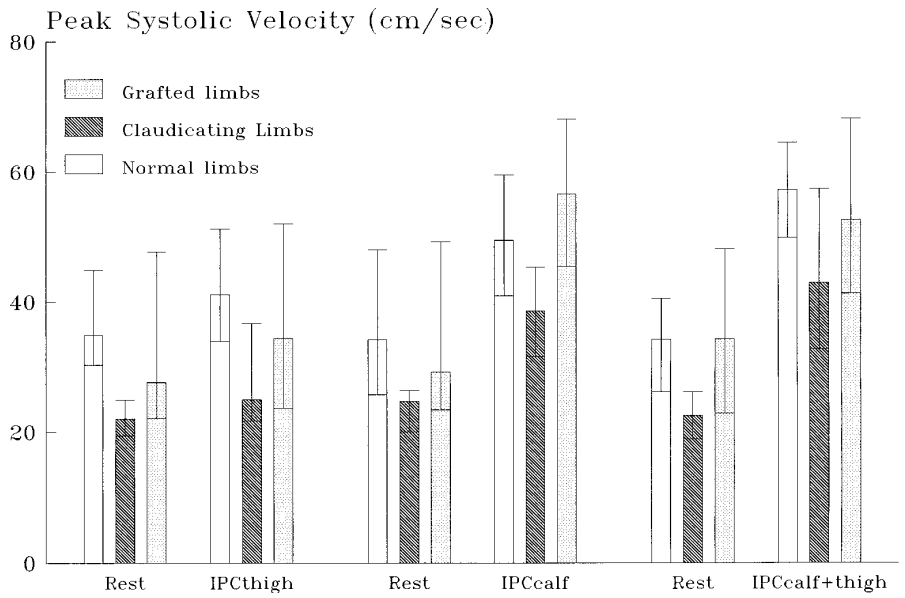

Fig 3. Effects of IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) on peak systolic velocity (PSV) in 16 limbs of healthy subjects, in 17 limbs with claudication, and in 16 limbs with infrainguinal bypass grafting. IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$ enhanced PSV in all groups ($P \leq .005$). $IPC_{calf + thigh}$ and IPC_{calf} produced higher PSV than IPC_{thigh} ($P < .003$). No difference was found between controls and grafted subjects at rest ($P > .05$). (See Results.)

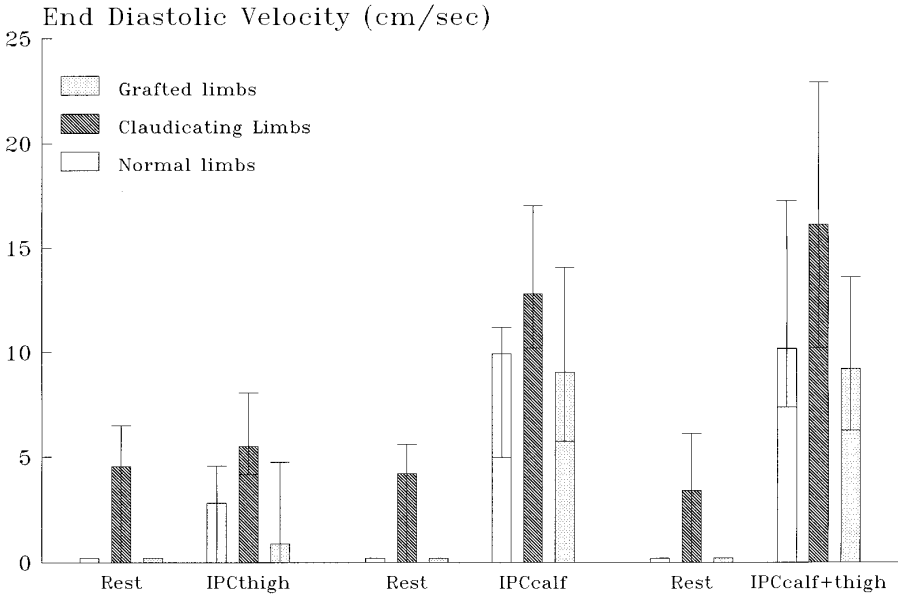

Fig 4. Effects of IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) on end diastolic velocity (EDV) in 16 limbs of healthy subjects, in 17 limbs with claudication, and in 16 limbs with infrainguinal bypass grafting. $IPC_{calf + thigh}$, IPC_{calf}, and IPC_{thigh} increased EDV in all groups ($P \leq .02$). EDV at rest was higher in claudicating limbs than in grafted ones or controls ($P < .001$). There was no difference between healthy and grafted limbs either in the resting sitting position or with IPC ($P > .05$). (See Results.)

venous pressure on limb dependency and resulting in an increase of the arteriovenous pressure gradient.[1,9-11] Pressure from an average of 60 mm Hg on sitting at rest decreases to 20 mm Hg with IPC_{foot}, to 14 mm Hg with IPC_{calf}, and to < 10 mm Hg with $IPC_{foot + calf}$, when pneumatic compression of 120 mm Hg is applied for 4 seconds 3 times per minute.[11] Changes in the arteriovenous pressure gradient may generate a flow increase of up to 70%.[12] The second putative mechanism is the tran-

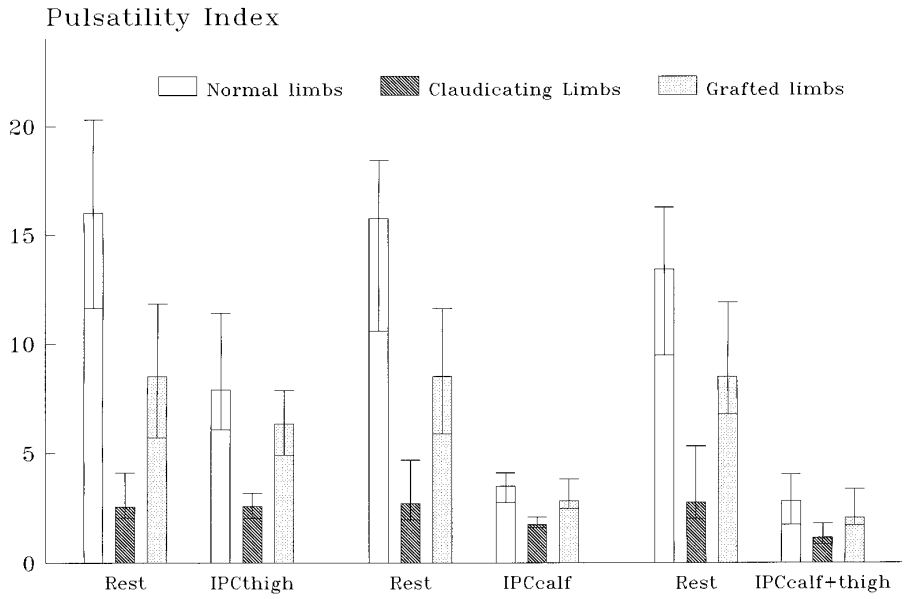

Fig 5. Effects of IPC (IPC_{thigh}, IPC_{calf}, and $IPC_{calf + thigh}$) on pulsatility index (PI) in 16 limbs of healthy subjects, in 17 limbs with claudication, and in 16 limbs with infrainguinal bypass grafting. $IPC_{calf+ thigh}$, IPC_{calf}, and IPC_{thigh} caused PI to decrease in all groups ($P < .03$). Baseline PI was lower in claudicants than in grafted subjects ($P \leq .01$), and PI in controls was higher than that in grafted limbs ($P \leq .004$), at all 3 resting time points. On intragroup comparison of the PIs at the 3 resting time points, no significant differences were found ($P > .05$). (See Results.)

sient suppression of the veno-arteriolar response which results from a decrease in the venous pressure immediately after delivery of a pneumatic impulse.[3,9] This response is mediated by means of a sympathetic axon reflex and results in attenuation of the precapillary peripheral vasoconstriction.[16-19] Thirdly, it has been suggested that promotion of the release of nitric oxide secondary to increased shear stress with IPC may lead to additional vasodilatation of the arterioles and precapillaries and to subsequent enhancement of peripheral arterial blood flow.[1-2,12,20] However, data in support of this have yet to be presented.

The median flow enhancement recorded in this study within the groups of claudicants and grafted arteriopaths did not exceed 60% with IPC_{thigh}; however, in a few limbs in these groups, flow increases far greater than this were recorded, exceeding 125% in some cases. This observation, and the greater than 100% increase in blood flow among healthy subjects, indicate that the only proven mechanism of flow enhancement—the decrease in arteriovenous pressure gradient—may be only part of the mechanism of flow enhancement with IPC_{thigh}. On application of $IPC_{calf + thigh}$ in the presence of a median flow augmentation exceeding 230% in both controls and arteriopaths, all of the aforementioned mechanisms may be involved.

Compression of the thigh causes maximal expulsion of the venous blood stored in the muscular veins of the profunda femoris system and the superficial femoral vein. The subsequent increase in flow with IPC_{thigh} would therefore be distributed both within the profunda femoris artery system and the superficial femoral artery with possibly greater flow enhancement occurring in the former. Provided that both vessels are patent, the effect of IPC_{thigh} would be more direct in the thigh than in the arterial foot and calf inflow. The entire venous capacitance of the thigh is exhausted on direct exertion of applied pressure of 120 mm Hg, enabling maximal arteriovenous pressure gradient enhancement in the profunda femoris circulation, in addition to the effects of endothelium-derived vasodilators. On the other hand, expulsion of venous blood from the superficial femoral vein alone would normally be expected to reduce the venous pressure of the dependent leg significantly, though probably not generating the levels provided with IPC_{calf} or $IPC_{foot + calf}$.

Enhancement of the arterial calf inflow with IPC_{thigh} offers the potential for several clinical applications. Patients with severe peripheral vascular disease may have their calf inflow enhanced by receiving IPC_{thigh} when the application of IPC in the calf or the foot is not feasible because of leg

infection, painful skin ulcers, recently performed surgery, unhealed wounds, dressings, or casts. IPC of the thigh can also be applied to enable flow enhancement additional to that generated with $IPC_{calf,}$ when IPC_{foot} cannot be used (foot gangrene, infection, ulcers, wounds, recent surgery). Just as IPC has shown long-term efficacy in improving the walking capacity of claudicants with superficial femoral artery occlusion,[4] IPC_{thigh} may improve thigh claudication secondary to severe profunda femoris artery disease (tandem lesions) not amenable to profundoplasty or percutaneous transluminal angioplasty. IPC_{thigh} also offers an alternative option of graft flow velocity enhancement, when for causes unrelated to the graft, flow attenuates and velocities decrease below the critical threshold for graft patency.

In conclusion, IPC applied to the thigh alone or in combination with IPC of the calf, is an effective method of native arterial and infrainguinal autologous graft flow enhancement. An increase in the EDV and a decrease in the PI during its application suggest that this effect may be attributable to a decrease in peripheral resistance. In the paucity of conservative methods available for lower limb blood flow enhancement in peripheral vascular disease, IPC_{thigh} with its leg inflow enhancing ability, alongside other IPC modes, may emerge as a reliable, noninvasive therapeutic discipline, improving claudication, assisting infrainguinal bypass graft patency, and providing arterial supply in support of wound healing. IPC_{thigh} adds to the armamentarium of currently known IPC options (foot or calf), promoting its flexibility, applicability, and efficacy.

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Original article

Haemodynamic effect of intermittent pneumatic compression of the leg after infrainguinal arterial bypass grafting

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Background: **Intermittent pneumatic compression (IPC) may increase blood flow through infrainguinal arterial grafts, and has potential clinical application as blood flow velocity attenuation often precedes graft failure. The present study examined the immediate effects of IPC applied to the foot (IPC_{foot}), the calf (IPC_{calf}) and to both simultaneously ($IPC_{foot+calf}$) on the haemodynamics of infrainguinal bypass grafts.**

Methods: **Eighteen femoropopliteal and 18 femorodistal autologous vein grafts were studied; all had a resting ankle : brachial pressure index of 0·9 or more. Clinical examination, graft surveillance and measurement of graft haemodynamics were conducted at rest and within 5 s of IPC in each mode using duplex imaging. Outcome measures included peak systolic (PSV), mean (MV) and end diastolic (EDV) velocities, pulsatility index (PI) and volume flow in the graft.**

Results: **All IPC modes significantly enhanced MV, PSV, EDV and volume flow in both graft types; $IPC_{foot+calf}$ was the most effective. $IPC_{foot+calf}$ enhanced median volume flow, MV and PSV in femoropopliteal grafts by 182, 236 and 49 per cent, respectively, and attenuated PI by 61 per cent. Enhancement in femorodistal grafts was 273, 179 and 53 per cent respectively, and PI attenuation was 63 per cent.**

Conclusion: **IPC was effective in improving infrainguinal graft flow velocity, probably by reducing peripheral resistance. IPC has the potential to reduce the risk of bypass graft thrombosis.**

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Introduction

Intermittent pneumatic compression (IPC) of the leg generates a significant increase in arterial blood flow in patients with peripheral vascular disease[1–3]. IPC of the foot (IPC_{foot}) increases arterial calf inflow by 50–90 per cent in arteriopaths, and by more in normal subjects[1,3]. A threefold to fourfold increase in the calf blood flow has been reported with foot and calf compression ($IPC_{foot+calf}$) in patients with superficial femoral artery occlusion[2,4]. The application of IPC for over 4 months ameliorates intermittent claudication and improves the ankle : brachial pressure index (ABPI)[5,6]. This is probably due to a flow-dependent promotion of collateral circulation[5,6].

Arterial grafts are complicated by early occlusion in up to 20 per cent of distal bypasses[7]. Failure that occurs within the first 2 or 3 days is usually due to poor selection or technical error; late failure within the first month results from a number of factors, including technical imperfection, persistent underlying disease and surface thrombogenicity of the graft[8,9]. It has been suggested that there is a critical threshold velocity required for ensuring graft patency in these early stages[10,11]. The likelihood of early thrombosis is high in a small-calibre graft placed into a high-resistance circulation, such as in the case of a femorodistal bypass graft in the presence of low flow velocities.

It was hypothesized that, analogous to its beneficial effect on native arterial blood flow, the application of IPC might also enhance arterial blood flow through an infrainguinal bypass graft. This might have clinical advantages, as low flow velocity precedes graft failure[12]. The aim of this study was to compare the immediate effects of IPC_{foot}, $IPC_{foot+calf}$ and IPC of the calf (IPC_{calf}) on arterial bypass graft haemodynamics in patients who had infrainguinal revascularization for ischaemia.

Patients and methods

Study groups

Graft flow velocities during IPC were measured in 16 patients with 18 femoropopliteal grafts (five above and 13 below knee) and in 18 patients with 18 femorodistal grafts (two peroneal, nine posterior tibial, five anterior tibial and two dorsalis pedis). There were 13 men and three women of mean(s.d.) age 65·9(9·6) years in the former group, and 15 men and three women aged 68·8(7·5) years in the latter group. All grafts were autologous vein. The femoropopliteal grafts had been inserted for a median of 17 (interquartile range 7·5–33) months and the femorodistal grafts for a median of 18 (interquartile range 12–26) months.

Patients who had an infrainguinal bypass were assessed by measurement of resting ABPI followed by graft surveillance using duplex imaging. Uncompromised grafts, defined by a resting ABPI of 0·9 or more, and no significant (50 per cent diameter or more) stenosis on duplex imaging, were recruited into the study.

Study design

The sequence of IPC application was subject to a crossover design. To eliminate bias from carry-over effects, the two study groups, comprising 18 legs each, had all six possible combinations of IPC sequences (IPC_{foot}–IPC_{calf}–$IPC_{foot+calf}$, IPC_{foot}–$IPC_{foot+calf}$–IPC_{calf}, etc.) applied to their legs and investigated evenly (three legs per sequence). These sequences were allotted numbers 1–18 at random from sealed envelopes, one for each new entry.

Examination and imaging protocol

Graft blood flow was studied using colour duplex ultrasonography with a linear-array 7·5-MHz probe. Subjects were scanned in the sitting position, with their legs dependent, slightly extended at the knees, and their feet resting on a low stool. Foot and calf pads enabling IPC delivery were applied, and a resting period of 15 min was allowed for flow stabilization, during which the subject remained seated.

Graft blood flow was measured first at rest, and then with IPC activated. Blood flow was studied on the sixth minute of IPC action. Data were retrieved within 5 s of IPC delivery and IPC was then switched off. After resting for 10 min, blood flow was reassessed. The second IPC mode was then engaged and flow measurement started on the sixth minute of pump action. Similarly, blood flow was measured before, and on delivery of the third IPC mode. At least three readings were obtained and then the mean was calculated. Internal diameter was obtained from longitudinal and cross-sectional graft views, in both systole and diastole on real-time B-mode imaging. Graft diameter was measured both at rest and with IPC (initial 5 s after compression). At least three measurements were made at each time point, and the mean was calculated. Spectral analysis of gated Doppler signals insonating the entire lumen at 60° enabled determination of mean velocity (MV). Positioning of the gate of the Doppler probe was meticulously maintained using physical landmarks. The MV was the mean of each of the velocity spectra occurring during an interval of at least four cardiac cycles; MV at rest and within 5 s of IPC was calculated with dedicated software tracing the waveform profiles. The reproducibility of the method has been reported previously[3].

Volume flow was calculated by multiplying MV by the cross-sectional area of the graft. Data gained from computer-assisted analysis of the profiles of spectral waveforms include pulsatility index (PI), and peak systolic (PSV) and end diastolic (EDV) velocities. Doppler waveforms containing aliasing, noise or wall motion were discarded. All haemodynamic evaluations were obtained by insonating grafts at the junction of the middle and distal thirds of the thigh by the same operator.

Impulse unit

All three IPC modes were delivered with an Art Assist 1000® unit (ACI, San Diego, California, USA). This mechanical pump consisted of a pneumatic impulse generator and two inflatable plastic pads designed to fit the foot and calf. Two large-bore tubes connecting the unit with each pad separately offered the versatility of isolating (with clamps) each pad from the other, thus enabling three IPC modes. The pump operated at the following presets: inflation pressure 120 mmHg, deflation pressure 0 mmHg, and inflation and deflation times 4 and 16 s respectively. With $IPC_{foot+calf}$, the onset of the foot impulse preceded that of the calf by 1 s.

Statistical analysis

Data analysis was performed using non-parametric statistics (Minitab 8.2; State College, Pennsylvania, USA) and Stat-View® 4·57 (Abacus Concepts, Berkeley, California, USA). Intragroup data were compared using the Wilcoxon signed rank test. Intergroup statistics were obtained using the Mann–Whitney *U* test.

Results

Mean velocity

Resting MV was similar in femoropopliteal and femorodistal grafts (*Fig. 1a*). Median MV increased by 39 per cent in femoropopliteal ($P = 0{\cdot}001$) and 36 per cent in femorodistal ($P < 0{\cdot}001$) grafts on IPC_{foot}, by189 per cent in femoropopliteal and 170 per cent in femorodistal grafts on IPC_{calf} (both $P < 0{\cdot}001$), and by 236 per cent in femoropopliteal and 179 per cent in femorodistal grafts on $IPC_{foot+calf}$ (both $P < 0{\cdot}001$). Increases in MV were similar in femoropopliteal and femorodistal grafts for any IPC mode. The MV on $IPC_{foot+calf}$ was higher than that on IPC_{calf} (femoropopliteal $P = 0{\cdot}019$; femorodistal $P = 0{\cdot}015$) and IPC_{foot} (both groups $P < 0{\cdot}001$). MV on IPC_{calf} was higher than that on IPC_{foot} (both groups $P < 0{\cdot}001$).

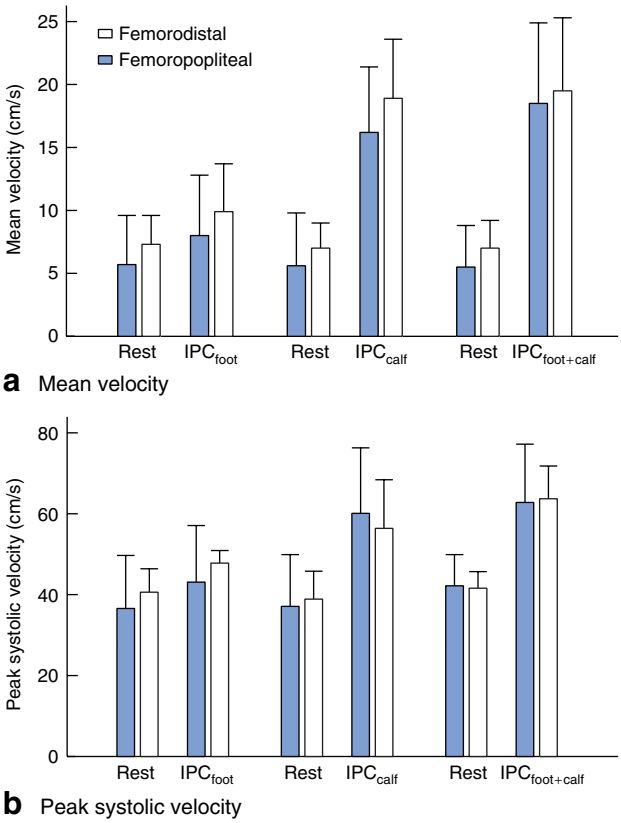

Fig. 1 Effects of intermittent pneumatic compression of the foot and calf ($IPC_{foot+calf}$), calf (IPC_{calf}) and foot (IPC_{foot}) on **a** mean velocity and **b** peak systolic velocity in 18 femoropopliteal and 18 femorodistal grafts. Values are expressed as median and interquartile range

Diameter

Baseline graft diameter, measured at a middle to distal thigh level, was slightly but not significantly greater in femoropopliteal than femorodistal grafts (*Table 1*). $IPC_{foot+calf}$ resulted in diameter increase in both groups ($P < 0{\cdot}001$ and $P = 0{\cdot}025$ respectively). The diameter increase with IPC_{calf} was marked in femoropopliteal grafts ($P = 0{\cdot}003$).

Volume flow

Resting volume flow was similar in the two graft types (*Fig. 2a*). Median volume flow increased by 76 per cent in both femoropopliteal ($P = 0{\cdot}002$) and femorodistal ($P < 0{\cdot}001$) grafts on IPC_{foot}, by 172 per cent in femoropopliteal and 186 per cent in femorodistal grafts on IPC_{calf} (both $P < 0{\cdot}001$), and by 182 per cent in femoropopliteal and 273 per cent in femorodistal grafts on $IPC_{foot+calf}$ (both $P < 0{\cdot}001$). Increases in volume flow were similar in femoropopliteal and femorodistal grafts for any IPC mode. $IPC_{foot+calf}$ generated a higher volume flow than IPC_{calf} (femoropopliteal $P = 0{\cdot}013$; femorodistal $P = 0{\cdot}006$) and IPC_{foot} (both groups $P < 0{\cdot}001$). Volume flow with IPC_{calf} was higher than that with IPC_{foot} (both groups $P < 0{\cdot}001$).

Peak systolic velocity

Baseline PSV was similar in femoropopliteal and femorodistal grafts (*Fig. 1b*). Median PSV increased by 17 per cent in femoropopliteal ($P = 0{\cdot}13$) and 18 per cent in femorodistal ($P = 0{\cdot}002$) grafts on IPC_{foot}, by 62 per cent in femoropopliteal and 45 per cent in femorodistal grafts on IPC_{calf} (both $P < 0{\cdot}001$), and by 49 per cent in femoropopliteal grafts and 53 per cent in femorodistal grafts on $IPC_{foot+calf}$ (both $P < 0{\cdot}001$). Increases in PSV were similar in femoropopliteal and femorodistal grafts for any IPC mode. PSV on $IPC_{foot+calf}$ was similar to that on IPC_{calf}. PSV on either $IPC_{foot+calf}$ or IPC_{calf} was higher than that on IPC_{foot} (both $P = 0{\cdot}002$).

End diastolic velocity

Baseline EDV was similar in femoropopliteal and femorodistal grafts. On IPC_{foot}, median EDV increased from 0 at baseline to 2·6 cm/s in femoropopliteal grafts and from 0 to 4·1 cm/s in femorodistal grafts (both $P < 0{\cdot}001$). On IPC_{calf}, EDV increased from 0 to 7·2 cm/s in femoropopliteal ($P < 0{\cdot}001$) and from 0 to 8·8 cm/s in femorodistal grafts ($P = 0{\cdot}001$). On $IPC_{foot+calf}$, median EDV increased from 0 to 8·3 cm/s in femoropopliteal grafts ($P < 0{\cdot}001$) and from 0 to 8·8 cm/s in femorodistal

Table 1 Effect of intermittent pneumatic compression on the luminal diameter of femoropopliteal and femorodistal grafts

	Femoropopliteal		Femorodistal	
	Diameter (cm)	*P**	Diameter (cm)	*P**
At rest	0·565 (0·505–0·636)	–	0·492 (0·444–0·557)	–
$IPC_{foot+calf}$	0·585 (0·520–0·663)	< 0·001	0·519 (0·448–0·593)	0·025
IPC_{calf}	0·578 (0·521–0·654)	0·003	0·521 (0·443–0·590)	0·330
IPC_{foot}	0·577 (0·511–0·656)	0·640	0·503 (0·433–0·550)	0·320

Values are median (interquartile range). Intermittent pneumatic compression was applied to the foot (IPC_{foot}), calf (IPC_{calf}) or both combined ($IPC_{foot+calf}$). **Versus* value at rest (Mann–Whitney *U* test). There were no significant differences between femoropopliteal and femorodistal graft luminal diameters under any condition tested.

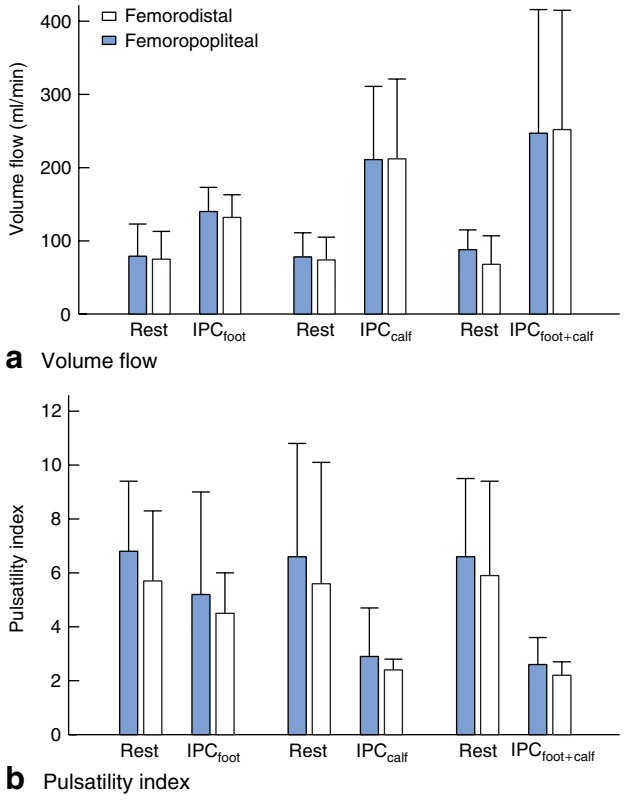

Fig. 2 Effects of intermittent pneumatic compression of the foot and calf ($IPC_{foot+calf}$), calf (IPC_{calf}) and foot (IPC_{foot}) on **a** volume flow and **b** pulsatility index in 18 femoropopliteal and 18 femorodistal grafts. Values are expressed as median and interquartile range

grafts ($P = 0·001$). Increases in EDV were similar in femoropopliteal and femorodistal grafts for any IPC mode. EDV on $IPC_{foot+calf}$ was similar to that on IPC_{calf}. EDV on IPC_{calf} or $IPC_{foot+calf}$ was higher than that on IPC_{foot} (both $P = 0·002$).

Pulsatility index

Baseline PI was similar in the two graft types (*Fig. 2b*). Median PI on IPC_{foot} decreased by 24 per cent in femoropopliteal ($P = 0·040$) and 21 per cent in femorodistal grafts ($P < 0·001$). On IPC_{calf}, median PI decreased by 56 per cent in femoropopliteal grafts and 57 per cent in femorodistal grafts (both $P < 0·001$). On $IPC_{foot+calf}$, median PI decreased by 61 per cent in femoropopliteal grafts and 63 per cent in femorodistal grafts (both $P < 0·001$). Changes in PI were similar in femoropopliteal and femorodistal grafts for any IPC mode. PI on $IPC_{foot+calf}$ was similar to that on IPC_{calf}. PI on IPC_{calf} and $IPC_{foot+calf}$ was lower than that on IPC_{foot} (both $P = 0·004$).

Discussion

This study has shown that IPC enhances flow through infrainguinal arterial bypass grafts, irrespective of the level of distal anastomosis. Flow was maximally increased in both femoropopliteal and femorodistal autologous vein grafts with $IPC_{foot+calf}$, followed by IPC_{calf}. IPC_{foot} was the least effective mode investigated, but still augmented flow significantly. Volume flow enhancement with any of the IPC modes was associated with a significant increase in mean flow velocity. In femoropopliteal grafts, volume flow enhancement with $IPC_{foot+calf}$ and IPC_{calf} was also associated with a significant increase in luminal diameter. This was noted in femorodistal grafts only on application of $IPC_{foot+calf}$. The MV within 5 s of $IPC_{foot+calf}$ application was 236 per cent higher than baseline in femoropopliteal and 179 per cent higher in femorodistal grafts.

All IPC modes produced a significant increase in EDV, and an equivalent decrease in PI, indicating a marked decrease in peripheral resistance[13,14]. A marker of impedance in the distal vascular bed, PI increases with vasoconstriction and decreases with vasodilatation[15].

An increase in the arteriovenous pressure gradient[1,4,16–18] is the main mechanism behind calf inflow

augmentation with IPC on sitting. IPC empties the deep veins and, until arterial flow refills them, venous pressure remains lower and the arteriovenous pressure gradient higher, causing blood flow to increase[1,4,16,17]. However, this mechanism alone cannot explain the magnitude of flow augmentation noted in normal subjects and patients with claudication[3,18]. Shear stress forces in the peripheral circulation upon pressure gradient and flow enhancement may promote release of endothelial factors, such as nitric oxide[1,2,18], whose vasodilatory activity on resistance arterioles should accentuate flow further[2,18,19]. Another mechanism enabling IPC to reduce arterial resistance involves the autoregulatory reflexes[4]. As veins empty, and for most deflation time (16 s), venous pressure falls to below 25 mmHg[16,17] . The venoarteriolar and myogenic reflexes are suspended, causing peripheral resistance to fall[20–23]. The greater flow enhancement with $IPC_{foot+calf}$ is linked to its superior venous haemodynamic performance[16].

Low flow velocities and graft surface thrombogenicity play cardinal roles in the pathophysiology of infrainguinal bypass graft failure. Bandyk *et al.*[12] demonstrated that a PSV lower than 40 cm/s in autologous infrainguinal grafts, compounded by low diastolic forward flow, increased the risk of graft thrombosis. A peroperative increase in coagulation factors, increased platelet reactivity and release of tissue thromboplastin in blood enhance thrombogenicity[24]. Low graft flow velocities in this environment can trigger platelet activation, secretion and aggregation, with subsequent thrombus formation and graft occlusion[25].

After infrainguinal graft insertion, hyperaemia develops upon perfusion, followed by an increase in outflow resistance[26]. EDV decreases and PI increases with reactivation of the capillary autoregulatory mechanisms in the distal circulation. With increasing peripheral resistance in this phase, flow velocities may decrease below a thrombotic threshold level[11]. Postoperative differences in peripheral resistance are increasingly perceived to affect the outcome of infrainguinal bypass grafting[26,27]. Revascularization under the combination of general and epidural anaesthesia appears to offer better graft patency than that carried out under general anaesthesia alone[26,27]. This may be the result of peripheral resistance reduction by epidural anaesthesia[26,27].

In the light of its haemodynamic effects, IPC offers the potential to prevent velocity attenuation after surgery. There is only a limited number of methods for enhancing flow in infrainguinal grafts. By inducing peripheral vasodilatation, prostaglandins cause a significant increase in graft blood flow[28]. Iloprost, a synthetic analogue of prostacyclin, generates a short-lived (20 min) decrease in peripheral resistance and a 52 per cent increase in graft flow when infused into femorodistal grafts before perfusion[29]. In a multicentre randomized trial, however, graft patency was not improved after 1 year of follow-up[29]. IPC has no notable side-effects. The median volume flow increase with IPC ranged from 76 per cent with IPC_{foot}, for femoropopliteal and femorodistal grafts respectively, to 182 and 236 per cent with $IPC_{foot+calf}$.

Application of IPC has certain limitations. Deep vein thrombosis and leg infection are contraindications, the flow increase wanes soon after IPC is stopped, and effective IPC use presupposes limb vein priming and thus limb dependency. Furthermore, IPC should not be applied directly to the anastomosis and surgical wounds after bypass grafting as this might compromise tissue healing. Different pneumatic cuffs and modes increase the flexibility of IPC: $IPC_{foot+calf}$ can be used in femoropopliteal grafts, IPC_{foot} in femorocrural grafts, and IPC_{calf} with narrow cuffs in femoropopliteal or femoropedal grafts. When the saphenous vein is harvested, long skin bridges improve the applicability of IPC. Provided that early ambulation is not unduly deferred, IPC may be used for intervals equal to those of sequential compression implemented for deep vein thrombosis prophylaxis.

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Integrity of venoarteriolar reflex determines level of microvascular skin flow enhancement with intermittent pneumatic compression

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Objective: **To investigate whether intermittent pneumatic compression (IPC) augments skin blood flow through transient suspension of local vasoregulation, the veno-arteriolar response (VAR), in healthy controls and in patients with peripheral arterial disease (PAD).**

Methods: **Nineteen healthy limbs and twenty-two limbs with PAD were examined. To assess VAR, skin blood flow (SBF) was measured using laser Doppler fluxmetry in the horizontal and sitting positions and was defined as percentage change with postural alteration [(horizontal SBF − sitting SBF)/horizontal SBF × 100]. On IPC application to the foot, the calf, or both, SBF was measured with laser Doppler fluxmetry, the probe being attached to the pulp of the big toe.**

Results: **Baseline VAR was higher in the controls 63.8 ± 6.4% than in patients with PAD (31.7 ± 13.4%, $P = .0162$). In both groups SBF was significantly higher with IPC than at rest ($P < .0001$). A higher percentage increase with IPC was demonstrated in the controls (242 ± 85% to 788 ± 318%) than in subjects with PAD, for each one of the three different IPC modes investigated (98 ± 33% to 275 ± 72%) with IPC was demonstrated. The SBF enhancement with IPC correlated with VAR for all three compression modes ($r = 0.58$, $P = .002$ for calf compression, $r = 0.65$, $P < .0001$ for foot compression alone, and $r = 0.64$, $P = .0002$ for combined foot and calf compression).**

Conclusion: **The integrity of the veno-arteriolar response correlates with the level of skin blood flow augmentation generated with intermittent pneumatic compression, indicating that this may be associated with a transient suspension of the autoregulatory vasoconstriction both in healthy controls and in patients with PAD. (J Vasc Surg 2008;48:1509-13.)**

Intermittent pneumatic compression (IPC) devices have been used to improve lower limb perfusion.[1-3] When assessed by laser Doppler flowmetry or duplex ultrasound, substantial increases in cutaneous and arterial blood flow during IPC application have been reported.[1,3-6] Different mechanisms through which IPC induces a circulatory augmentation have been discussed and studied. An undisputed mechanism is the reduction of venous pressure in the dependent foot by IPC, as blood is expelled from the foot and calf to the thigh.[7] This results in a greater arteriovenous pressure gradient and hence augmentation of arterial inflow. A putative mechanism is the transient suspension of local vasoregulation, the veno-arteriolar response (VAR).[8-12] In the sitting position, venous distension occurs, eliciting a precapillary vasoconstriction, and hence a decrease of capillary inflow. When blood is expelled from the veins of the lower extremities, venous pressure decreases and the precapillary sphincter dilates. This reduction in resistance may result in elevated arterial inflow. Previous studies have shown that the VAR in patients with peripheral arterial obstructive disease (PAD) is impaired, possibly as an adaptive response to a lower arterial perfusion and pressure.[9,11,13,14] Assuming that IPC produces blood flow increase by temporarily abolishing postural vasoconstriction, the effect of IPC might depend at least in part on the VAR. We hypothesized that the integrity of postural vasoregulation may correlate with blood flow augmentation on IPC application.

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MATERIALS AND METHODS

Study groups. The effects of IPC on foot skin blood flux were evaluated in 19 limbs of 15 healthy volunteers (controls) and in 22 limbs of 14 patients with intermittent claudication due to PAD.

Inclusion and exclusion criteria. All studied subjects underwent clinical examination and lower limb arterial and venous investigation that entailed duplex scanning and determination of ankle-brachial pressure indices (ABI) at rest and after exercise challenge on a treadmill. ABI was determined by dividing the higher ankle pressure (obtained from the dorsalis pedis or posterior tibial arteries) by the higher of the two brachial artery pressures after a 15-minute resting period and immediately after treadmill exercise challenge (3.8 km/h, 10% gradient, one minute) for the resting and post-exercise pressure indices, respectively. PAD patients had a long-term history of intermittent claudication (> two years and Rutherford

Table. Baseline characteristics of controls and patients with stable claudication

	Controls	*PAD*
Age (years)[a]	70 (65-83)	71 (61-84)
Gender ratio (M:F)	10:5	10:4
Risk factors, n (%)		
Smoking	8 (60)	9 (64)
Hypertension[b]	6 (40)	9 (64)
High cholesterol[c]	6 (40)	8 (57)
Ankle: brachial pressure index[a]	1.05 (1.02-1.10)	0.71 (0.52-0.85)

[a]Values are mean (range).
[b]Includes subjects on medications with normalized blood measurements at the time of investigation.
[c]Total cholesterol level > 240 mg/dL/ low-density lipoprotein level > 160 mg/dL/ high-density lipoproteine (<40 mg/dL)/ antilipemic medication.

stages I-III), that was confirmed by a reduced ABI at rest or after exercise (<0.9). Duplex ultrasonography documented infrainguinal arterial obstruction invariably pertaining to the superficial femoral. Patients with significant aortoiliac disease on duplex scan (>50% diameter stenosis) were excluded. Peak systolic velocity ratios ≥2.0 were used to account for (in the superficial femoral artery) or exclude (in the aortoiliac arterial segment) 50% or more luminal diameter stenosis.[15,16] Exclusion criteria included chronic venous disease (CEAP ≥ 2), diabetes mellitus, sensory neuropathy (clinically), previous lumbar sympathectomy, critical limb ischemia, gangrene/ulcerations and use of vasoactive drugs. There were no significant differences between the age- and gender-matched controls and patients with PAD with regard to cardiovascular risk factors (Table).

Examination and scanning protocol. Subjects were asked to withhold caffeine and nicotine for 12 hours prior to skin blood flow assessment. To assess peripheral postural vasoregulation, the veno-arteriolar response (VAR) was measured by determining skin blood flow (SBF) using laser Doppler fluxmetry in the horizontal and sitting positions prior to IPC application. The VAR was calculated as (SBF horizontal − SBF sitting)/SBF horizontal × 100 (percent). Afterward, all subjects were studied in the sitting position on a high examination couch, with their feet resting hanging off the floor. Foot and calf pads (cuffs) of the IPC system were applied gently, and a resting period of more than 20 minutes was allowed for flow stabilization, during which all subjects remained comfortably seated. IPC was then applied and skin flux measurements obtained, starting from the fifth minute of pump action. Subsequently, the IPC was switched off and the subjects were rested for more than 10 minutes, after which new resting skin flux estimations were obtained. The same protocol was followed to evaluate skin flux prior to and during delivery of the last IPC mode examined.

Skin blood flux/flow was obtained using Laserflo BPM 403 (Vasamedics, St. Paul, Minn) featuring a semiconductor gallium-aluminium-arsenide diode emitting a laser beam with a wavelength of 780 nm. The single point vertical angle laser probe was attached to the pulp of the big toe. The emitted monochromatic coherent light of the laser Doppler illuminates a tissue hemisphere with a radius of 0.1 to 1.4 mm interacting with the moving blood cells, and a proportion of them produce back-scattering and a fractional frequency shift, which is converted to skin blood flux readings. The mean skin blood flux was estimated by analyzing five-minute laser Doppler fluxmetry recordings on a thermosensitive strip obtained at a speed of 20 mm/min, a sensitivity of 10 to 100, and an average time of five seconds. Every effort was made to ensure good, consistent attachment of the probe to the skin with minimal motion artifacts. Tracings thought to result from suboptimal probe attachment were discarded, and measurements were repeated. All investigations were conducted in a noise-free, temperature-controlled environment (21°-23°C) under optimal resting conditions.

Impulse unit. Intermittent pneumatic limb compression was delivered with the Art Assist 1000 unit (ACI Medical, San Marcos, Calif). This is a mechanical pneumatic pump built around a pneumatic impulse generator which consists of an electrically driven air compressor and an air reservoir venting intermittently into two inflatable plastic pads designed to fit the foot and calf. One large-bore elastic tube connects the unit with each one of the pads. Investigation throughout the study was conducted with the pump operating at the following preset parameters: maximum inflation pressure 120 mmHg, minimum deflation pressure 0 mmHg; inflation rise time 0.3 seconds and inflation time four seconds followed by 16 seconds of deflation (0 mmHg), resulting in three compression cycles min-1. Laser Doppler readings were obtained within the 16 seconds of pressure release over a total time period of five minutes of IPC application.

Statistics. Values are shown as mean ± SEM. Analysis was performed using nonparametric statistics on StatView 4.57 (Abacus Concepts, Berkeley, Calif). For intra-group comparison of the effects of different modalities of IPC, the Friedman test was used. For inter-group comparison, the Mann-Whitney U test was applied. The Spearman rank correlation was used to calculate the relation between VAR and skin blood flow augmentation on IPC.

RESULTS

Skin blood flow (SBF) in the horizontal position was similar between controls and PAD (6.8 ± 2.8 to 7.1 ± 1.5 arbitrary units, $P = .68$), whereas SBF in the sitting position was significantly lower in the controls (2.1 ± 0.8 vs. 5.3 ± 1.6 arbitrary units, $P = .01$) (Fig 1). This resulted in a greater VAR in the controls (63.8 ± 6.4%) vs the PAD patients (31.7 ± 13.4%) ($P = .02$) (Fig 2). All three modes of pressure application produced higher levels of SBF compared with the resting values in both groups ($P < .0001$). The percentage of SBF increase on IPC was lowest with calf compression alone (242 ± 85% in controls and 98 ± 33% in PAD patients) (Fig 3). Higher levels of SBF percentage increase were achieved in the control group with foot compression and combined foot and calf compression (697 ± 205% and 788 ± 318%

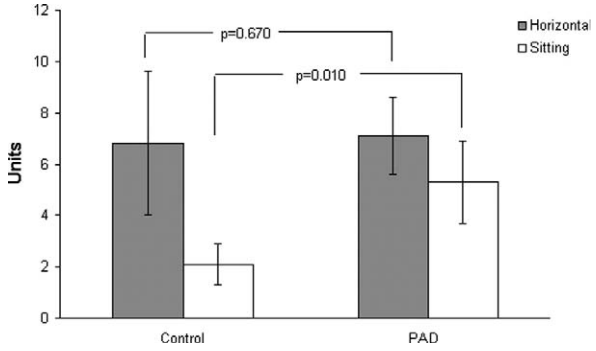

Fig 1. Pedal skin blood flow in recumbent and dependent position in controls and patients with peripheral arterial disease.

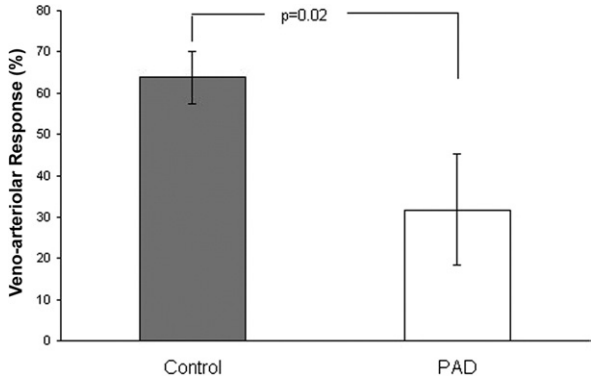

Fig 2. Veno-arteriolar response in controls and patients with peripheral arterial disease.

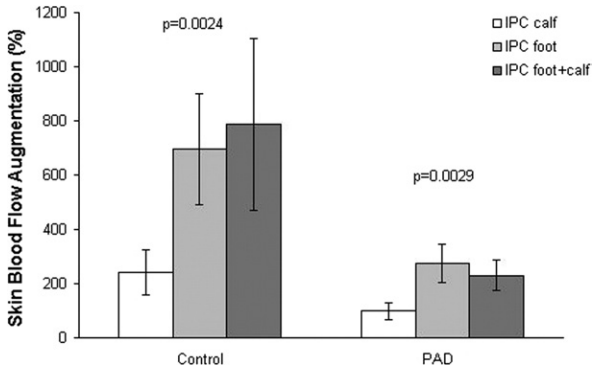

Fig 3. Percentage skin blood flow increase on intermittent pneumatic compression applied to the foot, the calf or both in healthy controls and claudicants.

respectively). In PAD patients with foot compression alone or with combined foot and calf compression, the percentage increases were 275 ± 72% and 230 ± 57% respectively (Fig 3). SBF with calf, foot, and combined foot and calf compression were significantly higher in the controls compared with PAD patients ($P = .005$, $P = .0158$, and $P = .006$).

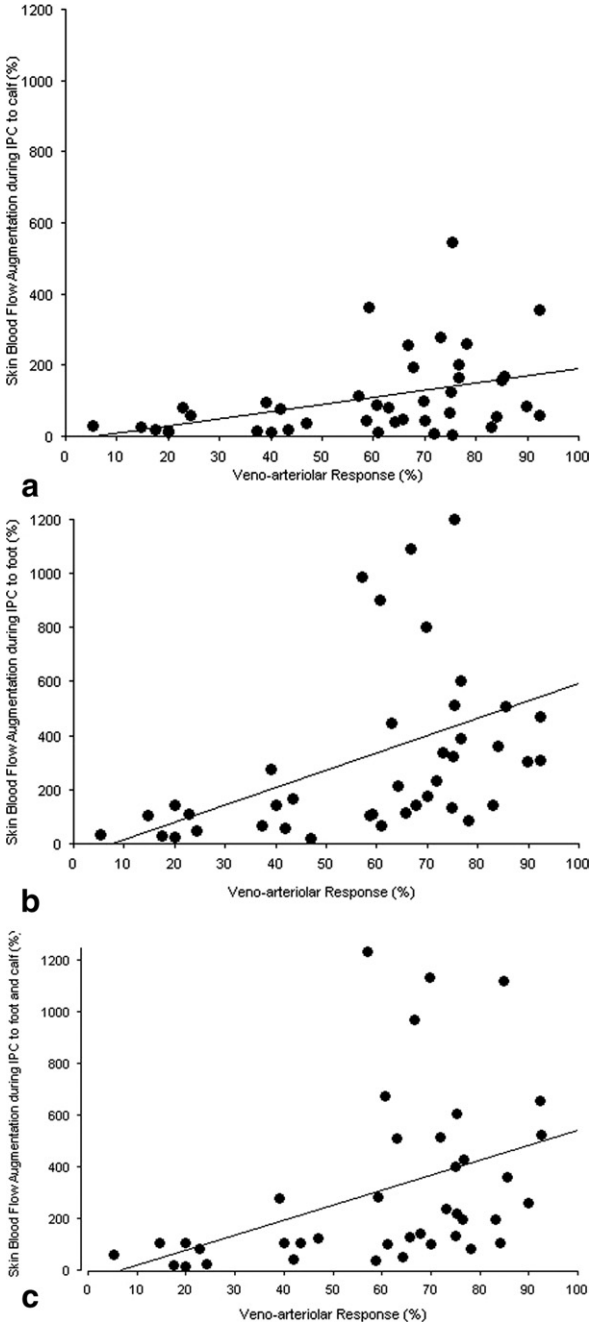

Fig 4. Spearman correlations between veno-arteriolar response and skin blood flux augmentation (percentage increase) with intermittent pneumatic compression applied to **(a)** the calf (r = 0.58, $P = .002$), **(b)** the foot (r = 0.65, $P < .0001$), or **(c)** foot and calf (r = 0.64, $P = .0002$), both in healthy controls and claudicants.

There was a significant correlation between the VAR and the SBF augmentation (percentage SBF increase) with all three IPC modes when the controls and the PAD patients were grouped together: r = 0.58, $P = .002$ for calf compression (Fig 4, *a*), r = 0.65, $P < .0001$ for foot

compression (Fig 4, *b*), and r = 0.64, $P = .0002$ for foot and calf compression (Fig 4, *c*). When analysis was performed for the PAD patients only, the VAR correlated well with SBF augmentation on foot (r = 0.69, $P = .002$) and foot and calf (r = 0.65, $P = .0035$) compression, but not on calf compression alone (r = 0.36, $P = .105$). In the control subjects, there was a correlation between the VAR and the augmentation of SBF with IPC, when delivered to the foot (r = 0.55, $P = .017$) and the calf (r = 0.58, $P = .012$), but not when delivered to foot and calf combined (r = 0.45, $P = 0.15$).

DISCUSSION

The study data show that the greater the magnitude of the veno-arteriolar response (VAR) the higher the percentage increase in skin blood flow with IPC, suggesting that a transient attenuation of the VAR during IPC application might be one of the mechanisms through which the latter generates higher levels of blood flow in the lower limb.

Impairment of peripheral sympathetic postural autovasoregulation, the local veno-arteriolar response, has been documented in diabetes mellitus, diabetic and alcoholic neuropathy, as well as in PAD.[8,9,13,14] Recent work has shown that the VAR becomes increasingly impaired with PAD progression but is regained after successful bypass grafting or endovascular treatment, suggesting re-adjustment of peripheral resistance.[9,17,18] Improved arterial leg inflow after bypass grafting or endovascular angioplasty is associated with a reversal of peripheral vasodilatation and a decrease in both arterial calf inflow and skin flux on dependency.[17,18] Our data is in accordance with previous studies demonstrating an impaired VAR in patients with intermittent claudication due to PAD.[9,17,19]

In keeping with previous reports, we also found lower levels of skin blood flow augmentation with IPC in patients with PAD than in healthy controls.[1,4,20-22] Different physiologic mechanisms through which IPC induces its flow augmentation effects have been proposed. As previously noted, by expelling the blood from the dependent leg, IPC increases the arterio-venous pressure gradient generating arterial inflow augmentation.[6,7] The increased arterio-venous pressure gradient, however, cannot explain by itself the high level of flow augmentation with IPC observed both in normal limbs and limbs with PAD. A decrease in peripheral resistance has been reported, but the physiologic mechanism involved is not fully understood.[1,3] Increase in the arterio-venous pressure gradient results in release of vasodilatory endothelium-dependent factors in response to shear stress, either by way of increased arterial leg inflow and/or by the transmitted compression impulses.[23,24] Recent work has demonstrated 2- to 2.5-fold up regulation of the endothelial nitric oxide synthase in uncompressed upstream muscle secondary to IPC and its suppression by nitric oxide synthase inhibitor one hour after IPC.[23]

As venous pressure decreases to 25 mmHg or less during most of the deflation time (16 seconds), it could be hypothesized that the veno-arteriolar reflex during the application of IPC is transiently suspended, with subsequent attenuation of peripheral resistance.[14,25] Our findings suggest that transient suspension of the precapillary vasoconstriction (VAR) is one of the mechanisms by which blood flow would improve with IPC. Additionally, we could demonstrate that a higher skin blood flow on application of IPC is obtained in limbs with more pronounced and hence larger veno-arteriolar responses as shown by a significant correlation between the VAR and skin blood flow augmentation with IPC. In the dependent limb, precapillary vasoconstriction induced by an increase in venous pressure is a physiological mechanism to regulate the hydrostatic arterial pressure augmentation offering protection to the capillary bed. Precapillary vasoconstriction increases peripheral resistance resulting in a lower skin blood flow on dependency. Skin blood flow is lower in healthy limbs than in limbs with PAD in the depending position, as shown in our study and other previous reports.[17,18,26] Therefore, the higher percentage increase in SBF with IPC among healthy limbs mirrors a greater vasodilatory capacity secondary to a stronger vasoconstrictory status in the resting dependent limb. Owing to arterial obstruction at the femoro-popliteal segment and hence the reduced pressure in the distal arteries, the lower VAR is a physiological vascular adaptation in PAD.[9,11]

The present study enhances our insight into these pertinent physiologic mechanisms. Understanding the mechanisms involved in blood flow augmentation with IPC is important for its clinical application. In patients with other disorders that impair VAR (ie, diabetes or chronic venous disorders), the flow enhancing mechanisms of IPC might be different or have a modified effect.[8,27,28] In addition, our understanding of the mechanisms through which IPC enhances blood flow might increase its use, particularly as a recent study has shown an improved limb salvage rate attributable to the use of IPC in patients with critical limb ischemia.[2] With a growing elderly population and an increase in metabolic syndrome, the prevalence of PAD will rise.[29] Different therapeutic modalities are needed to treat patients with limb ischemia. Parallel to surgical and endovascular interventions, there is a need for additional conservative therapeutic measures.[30,31] Further studies need to investigate whether the combination of revascularisation and IPC improves the management of PAD patients. Current knowledge suggests that shear stress and nitric oxide are crucial for angiogenesis.[32-34] In patients with impaired walking distance or even critical limb ischemia, peak shear stress is poor owing to proximal arterial obstruction. Therefore, the application of IPC with a view to enhancing shear stress and arterial leg inflow augmentation might promote angiogenesis.

Limitations of the present study include the small population examined. Also, we evaluated only patients with intermittant claudication, and these data are not directly applicable to patients with critical limb ischemia as the VAR is abolished.[13,14] Because we excluded patients with diabetes mellitus knowing that this disease itself might impair VAR, the relation between VAR and blood flow augmentation by IPC in such patients remains unclear.

In conclusion, skin blood flow augmentation with IPC is associated with a transient suspension of the veno-arteriolar

vasoconstriction of the precapillary sphincter. In support of prior pertinent data, this study reinforces the potential of IPC to emerge as an important mechanical device enhancing skin microcirculation in PAD.

AUTHOR CONTRIBUTIONS

Conception and design: MH, KD
Analysis and interpretation: MH, KD, TW, HHK, SS, EK
Data collection: KD, MH
Writing the article: MH, TW, KD
Critical revision of the article: EK, SS, KD
Final approval of the article: MH, TW, HHK, SS, EK, KD
Statistical analysis: MH, KD
Obtained funding: MH
Overall responsibility: MH, KD

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Long-term effects of endovascular angioplasty on orthostatic vasocutaneous autoregulation in patients with peripheral atherosclerosis

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Objective: **To test the hypothesis that endovascular revascularization of femoropopliteal lesions improves the impaired venoarteriolar response (VAR) in patients with atherosclerosis.**

Methods: **We prospectively compared VARs in 15 healthy controls (18 legs) and 14 patients (17 legs) with mild to moderate peripheral arterial disease before and after successful peripheral endovascular angioplasty of femoropopliteal lesions. In all subjects, foot skin blood flow was assessed by laser Doppler flowmetry in the horizontal (HBF) and sitting (SBF) positions. VAR was calculated as (HBF − SBF)/HBF × 100.**

Results: **In patients with peripheral arterial disease, mean HBF (in arbitrary units [AU]; mean ± SD) was similar before (25.6 ± 15.3 AU) and after (27.0 ± 16.4 AU) angioplasty ($P = .67$), whereas SBF was significantly lower after than before the endovascular procedure (11.6 ± 7.7 AU to 18.4 ± 14.1 AU; $P < .05$). Intragroup differences between SBF and HBF were significant before and after angioplasty ($P < .001$). VAR was higher after angioplasty (55.1% ± 21.2%) compared with VAR before intervention (33.4% ± 20.2%; $P = .015$). Although VAR increased after the intervention, VAR was still lower than in healthy controls (68.4% ± 20.5%; $P = .025$). During the 6 months of follow-up, the ankle-brachial index and VAR remained unchanged ($P > .05$).**

Conclusions: **Patients with mild to moderate peripheral arterial disease have an impaired orthostatic autoregulation that improves after successful endovascular revascularization of femoropopliteal obstructive lesions. The effect on VAR is sustained in the absence of restenosis. (J Vasc Surg 2006;44:993-7.)**

The autonomic nervous system regulates postural vasoregulation, which is mediated through a sympathetic axon reflex that acts on cutaneous, subcutaneous, and muscular arterioles.[1-4] A postural change from the horizontal to the recumbent or upright position increases venous pressure and elicits precapillary vasoconstriction, known as the venoarteriolar response (VAR). The VAR is thought to play a protective role in vascular homeostasis by preventing the capillary bed from a sudden increase in pressure and filtration.[5-8]

Different conditions such as chronic venous insufficiency,[5] diabetic autonomic neuropathy,[6] administration of calcium antagonists,[7] and aging[8] impair VAR. Severe dysfunction of the VAR occurs in peripheral arterial disease (PAD) with either stable claudication or critical limb ischemia.[9,10]

Skin blood flow, which is reduced in the feet of healthy individuals in the sitting position when compared with the horizontal position, is higher in the dependent position in patients with obstructive arterial disease than in healthy controls.[11,12] In the presence of PAD, the VAR is attenuated.[9,10] Because of an impaired VAR, many PAD patients with severely limited arterial inflow show skin redness on dependency, which reflects a higher skin blood flow.[10] Although contradictory results have been published about VAR in patients with stable claudication,[1,2,13] a recent study demonstrated that successful surgical revascularization causes short-term improvement of VAR in patients with subcritical or critical lower limb ischemia.[14] Whether this is also applies for patients with mild to moderate peripheral atherosclerosis, whether percutaneous endovascular revascularization affects VAR, and whether revascularization has long-term effects on VAR are unknown.

METHODS

Human subjects. This was a cohort study conducted in a tertiary referral university hospital consisting of two groups. Fourteen consecutive patients (17 legs investigated) were included with stable intermittent claudication (Rutherford stages I to III) caused by superficial femoral or popliteal artery obstructions who were scheduled for elective endovascular angioplasty and who met the inclusion criteria. Fifteen healthy subjects (18 legs investigated) without PAD or venous or lymphatic disease were recruited through advertisements. The institutional ethics committee approved the study. The inclusion and exclusion criteria are

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Table I. Inclusion and exclusion criteria

Inclusion criteria
No clinical symptoms or signs of peripheral arterial disease (control)
Ankle-brachial index exceeding 0.9 (control group)
Initial claudication distance 100-300 m (claudication group before angioplasty)
Successful angioplasty (on angiogram and duplex sonography; claudication group)
Exclusion criteria
Evidence of sensory neuropathy/diabetes mellitus
Use of vasoactive medications
Chronic venous insufficiency
Previous lumbar sympathectomy
Critical limb ischemia
Gangrene/ulcerations

Table II. Demographic details

Variable	*Controls (n = 15)*	*Claudication (n = 14)*
Age (y)*	70 (65-83)	71 (61-84)
Sex ratio (M:F)	10:5	10:4
Risk factors		
Smoking†	8 (6)	9 (4)
Hypertension‡	6	9
High cholesterol	6	8
Ankle-brachial pressure index*	1.05 (1.02-1.10)	0.71 (0.52-0.85)§
After angioplasty		0.89 (0.72-1.10)

*Values are mean (range).
†Values in parentheses are numbers of active smokers at the time of investigation.
‡Includes subjects on medications with normalized blood measurements at the time of investigation.
§Claudicants before angioplasty.

listed in Table I, and demographic data are given in Table II. Control subjects were recruited to match the patients for age and sex. The prevalence of risk factors was significantly different between patients and controls. All subjects were asked to refrain from caffeine-containing drinks and smoking for at least 12 hours before the investigation. Risk factors in each group and ankle-brachial pressure indices (ABIs) are presented in Table II.

All subjects underwent the following examination protocol. (1) A full medical history was taken, and a physical examination was performed. (2) Venous color duplex imaging was used to detect chronic venous insufficiency as described previously.[15] (3) In patients, angiography was performed before and after angioplasty. (4) Control duplex imaging was used to evaluate femoropopliteal patency after revascularization.[16] (5) Laser Doppler fluxmetry was performed to determine skin blood flow in the horizontal (HBF) and recumbent positions (Laserflo BPM403; Vasamedics, St Paul, Minn). The probe was secured at the tip of the big toe by using ring-shaped double-sided adhesive tape. Measurements of skin blood flow were made after a 20-minute resting period in a temperature-controlled room (21°C-22°C). The recorded chart was set at 20 mm/min (Brush 2600S Recorder; Gould, Cleveland, Ohio).

Measurements of resting skin HBF were averaged over 10 minutes and expressed in arbitrary flow units (AU). The subjects were then placed in the upright sitting position with their feet in a stable dependent position. The probe remained fixed at the tip of the big toe. Sitting blood flow (SBF) was calculated during the 10 minutes after the initial 10 minutes of sitting to allow for stabilization of the skin blood flow. The VAR was calculated as (HBF − SBF)/HBF × 100. Laser Doppler fluxmetry enables noninvasive measurement of cutaneous blood flow and its changes arising from alteration of posture.[10,14] Red blood cell flow is proportional to the concentration and velocity of red blood cells flowing in the capillaries. These variables are influenced significantly by the density of capillaries, known to vary in the skin, affecting the spatial and temporal variability of red blood cell flow measurements. By obtaining red blood cell flow from the same position on the foot during a single examination setting and expressing the results as ratio flow values, the VAR can be estimated reproducibly because differences in the temporal and spatial domains are nullified.[14]

Statistics. Results are presented as means ± SD. Statistical analyses were performed with StatView 4.57 (Abacus Concepts, Inc, Berkley, Calif). Data obtained from different positions were compared by using the Wilcoxon signed rank test. Intergroup (controls vs PAD) comparisons were performed with the Mann-Whitney *U* test. Spearman rank correlation was used to analyze a correlation between ABI and VAR. $P < .05$ was considered significant.

RESULTS

In both patients and healthy controls, the skin HBF was significantly higher than SBF. Controls had lower skin blood flow in both positions compared with PAD patients before intervention (HBF: 7.0 ± 2.9 AU vs 25.6 ± 15.3 AU, $P < .001$; SBF: 2.1 ± 0.8 AU vs 18.4 ± 14.4 AU, $P < .001$). Similarly, decreases in skin blood flux on sitting (VAR) were significantly higher in controls (68.4% ± 20.5%) than in PAD patients before angioplasty (33.4% ± 20.2%; $P < .001$).

In the PAD group, percutaneous revascularization did not affect HBF (27.0 ± 16.4 AU; $P = .56$) but significantly decreased SBF (11.6 ± 7.7 AU; $P < .001$). Although angioplasty resulted in a significant decrease in skin SBF, the VAR was still lower in the PAD group (55.1% ± 21.2%) than in controls (68.4% ± 20.5%; $P < .05$; Figs 1 and 2).

During follow-up, the PAD group showed a nonsignificant tendency toward higher levels of both HBF (32.7 ± 23.7 AU) and SBF (17.8 ± 8.7 AU) after 3 months and at 6 months (HBF, 35.6 ± 19.2 AU; SBF, 17.2 ± 10.9 AU; $P > .05$). However, VAR remained unchanged during the follow-up, at 55.7% ± 18.2% and 52.6% ± 18.3% after 3 and 6 months, respectively ($P = .56$; Fig 3). Similarly, ABI did not change during the 6 months (0.92 ± 0.21 at 3 months and 0.88 ± 0.18 at 6 months; $P = .67$; Fig 4). ABI decreased in five limbs of four patients, but none of

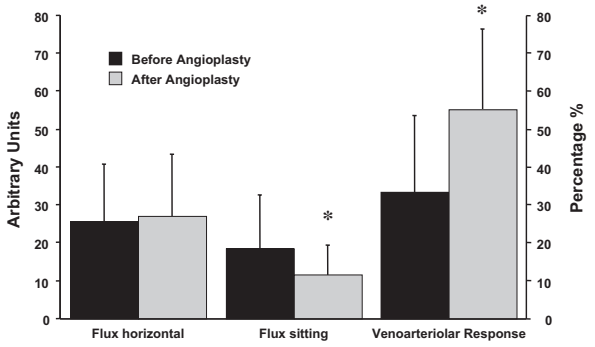

Fig 1. Effect of angioplasty on skin blood flow and vasocutaneous autoregulation. Skin blood flow in supine (Flux supine) and sitting (Flux sitting) position and the decrease in flux on sitting (venoarteriolar response; VAR) in patients with stable intermittent claudication. Measurements were obtained before and after successful percutaneous angioplasty of femoro-popliteal obstructions. $*P < .05$ before versus after angioplasty.

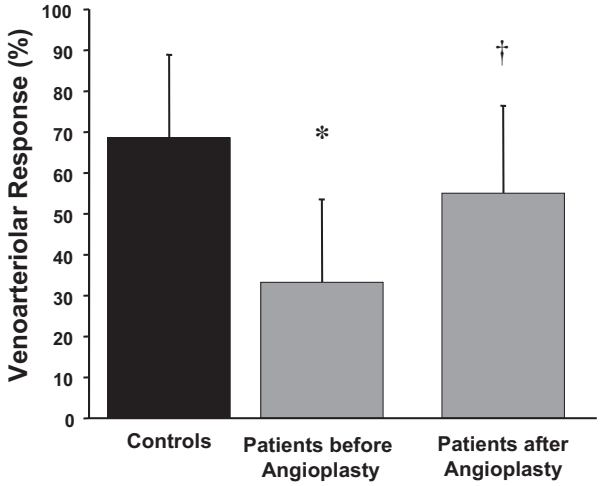

Fig 2. Vasocutaneous autoregulation in controls and in patients with peripheral arterial disease. Decrease in skin blood flow on sitting (venoarteriolar response; VAR) in healthy controls compared to patients with stable intermittent claudication before and after femoro-popliteal angioplasty. $*P < .05$ versus controls; $†P < .05$ before versus after angioplasty.

the patients reported worsening of claudication or required percutaneous intervention. There was no correlation between the changes in VAR and ABI ($r = 0.18$; $P = .46$).

DISCUSSION

The peripheral vasoregulatory response to orthostasis is attenuated in patients with critical leg ischemia.[1,4,10,17] However, the data available until now on autonomic function of patients with moderate PAD have been contradictory.[1,2,10,13] A recent study showed improvement of this response in PAD patients after successful surgical infrainguinal bypass grafting within 7 days after surgery.[14] We now report that endovascular reconstruction of femoropopliteal lesions in patients with noncritical PAD improves the VAR and that this beneficial effect is sustained during a follow-up period of 6 months.

First described by Gaskell and Burton[18] and later described by Henriksen, Paaske, and associates,[1,2,4] the VAR is due to a local axon reflex on the arterioles in response to passive venous distension. The result is an increase in peripheral resistance and a decrease in blood flow.[6,7] This vasoconstrictive response preserves systemic blood pressure in different postures and prevents capillary pressure increases, interstitial fluid leakage, and edema formation.[1,2,4,6,7] Laser Doppler flow measurements have been established as a noninvasive method for the investigation of microcirculatory flow in health and disease. As red blood cell flow at the same position in the supine and sitting positions is measured, temporal and spatial variability are nullified. This method allows reproducible testing of vascular microcirculatory function and dysfunction.[5,9,10,19]

This study demonstrates that patients with noncritical PAD with stable intermittent claudication due to femoropopliteal obstructions have a significantly greater flux in the dependent position than healthy age- and sex-matched subjects. This indicates that vasocutaneous autoregulation is already impaired at an early stage of peripheral vascular disease because of either local neurologic damage and/or physiological resetting of arterioles, possibly to optimize perfusion in the ischemic leg.

A previous short-term study demonstrated that autoregulation returns to normal within 7 days after infrainguinal bypass surgery performed for noncritical limb ischemia.[14] Because nerve tissue repair requires much longer (up to several months), it seems likely that the mechanisms involved require a physiological resetting rather than nerve regeneration. In this study, there was no further improvement of autoregulation between the first and sixth months after successful revascularization. This supports previous findings that local vasoregulation is pressure and/or flow sensitive to maintain local tissue perfusion.[14]

The results of our study have possible clinical implications. The measurements of skin blood flow by laser Doppler fluxmetry before or after an intervention or during follow-up may provide additional information about the degree of improvement of vascular autoregulation in patients with noncritical limb ischemia. The findings of this study may also help us to understand the acute and chronic pathophysiological mechanisms involved in cutaneous vasoregulation. Our study, for the first time, to our knowledge, shows a long-term beneficial effect of percutaneous transluminal interventions on peripheral vasoregulation of the lower limb. Additionally, VAR may reflect the functional reserve capacity, which has been proposed as one mechanism through which intermittent pneumatic compression may improve peripheral arterial macrocirculation and microcirculation in healthy controls and patients with PAD.[20-22] Indeed, intermittent pneumatic compression (of the lower limb) improved peripheral blood flow up to

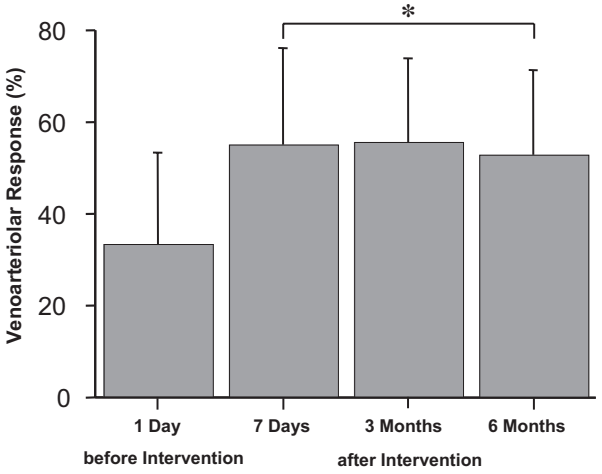

Fig 3. Long term effect of angioplasty on vasocutaneous autoregulation in patients with peripheral arterial disease. Decrease in skin blood flow on sitting (venoarteriolar response; VAR) in patients with stable intermittent claudication before and six months after femoro-popliteal angioplasty. * $P < .05$ for follow-up after angioplasty.

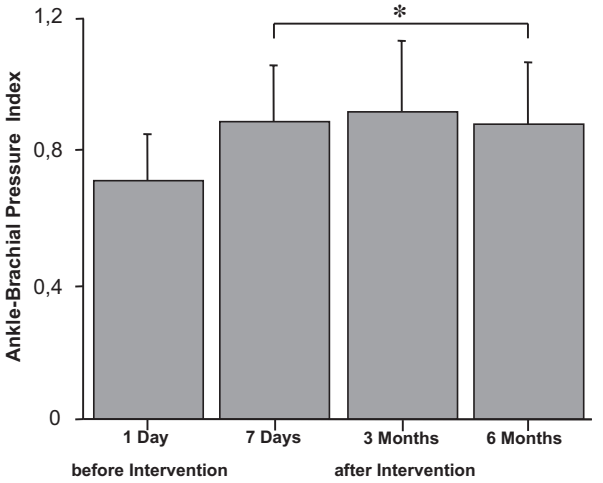

Fig 4. Long-term effect of angioplasty on ankle-brachial pressure indices in patients with peripheral arterial disease. Ankle-brachial pressure indices in patients with stable intermittent claudication before and six months after femoro-popliteal angioplasty. * $P < .05$ for follow-up after angioplasty.

300% when measured by laser Doppler fluxmetry, showing higher increases in healthy controls and patients after successful infrainguinal bypass grafting.[20-22] When compression in the dependent position empties the venous pooling, the venoarteriolar reflex is attenuated,[23] and local skin perfusion increases via dilation of the precapillary sphincter. Given the findings of this study, the combination of femoropopliteal angioplasty and intermittent pneumatic compression may have synergistic effects, which merits further experimental and clinical studies.

This study is limited by the small number of patients investigated and the fact that only patients with mild to moderate PAD were included. However, VAR assessment requires additional instruments and examination time, and at present there is no indication to routinely perform VAR measurement in addition to ABI measurements. The study also did not include patients with diabetes, venous hypertension, or critical limb ischemia so that we examined a rather homogenous group to exclude confounding factors that may impair VAR.[5,10,13] Therefore, these findings are likely to reflect a pathophysiological mechanism in patients with only peripheral atherosclerosis.

In conclusion, patients with mild to moderate peripheral atherosclerotic disease already exhibit impaired orthostatic local autoregulation at a stage of noncritical limb ischemia. Percutaneous angioplasty of femoropopliteal obstructions improves peripheral vasoregulation, possibly through a flow- and/or pressure-related mechanism. The observation that the improvement in VAR is sustained 6 months after treatment also suggests a possible long-lasting positive effect of angioplasty on orthostatic autoregulation in the absence of restenosis.

AUTHOR CONTRIBUTIONS

Conception and design: MJH
Analysis and interpretation: MJH
Data collection: MJH, GG
Writing the article: MJH
Critical revision of the article: AS
Final approval of the article: MB, BRA-V
Statistical analysis: MJH, MB
Obtained funding: BRA-V
Overall responsibility: MJH

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Successful lower extremity angioplasty improves brachial artery flow-mediated dilation in patients with peripheral arterial disease

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Introduction: **Peripheral arterial disease (PAD) is associated with systemic impaired flow-mediated dilation (FMD) and increased risk for cardiovascular events. Decreased FMD may be caused by a decrease in arterial shear stress due to claudication and inflammation due to muscle ischemia and reperfusion. We assumed that endovascular revascularization of lower limb arterial obstructions ameliorates FMD and lowers inflammation through improvement of peripheral perfusion.**

Methods: **The study was a prospective, open, randomized, controlled, single-center follow-up evaluation assessing the effect of endovascular revascularization on brachial artery reactivity (FMD) measured by ultrasound, white blood cell (WBC) count, high-sensitive C-reactive protein (hs-CRP), and fibrinogen. We investigated 33 patients (23 men) with chronic and stable PAD (Rutherford 2 to 3) due to femoropopliteal obstruction. Variables were assessed at baseline and after 4 weeks in 17 patients (group A) who underwent endovascular revascularization and best medical treatment, and in 16 patients (group B) who received best medical treatment only.**

Results: **FMD did not differ between group A and B (4.96% ± 1.86% vs 4.60% ± 2.95%; $P = .87$) at baseline. It significantly improved after revascularization in group A (6.44% ± 2.88%; $P = .02$) compared with group B at 4 weeks of follow-up (4.53% ± 3.17%; $P = .92$), where it remained unchanged. The baseline ankle-brachial index (ABI) was similar for group A and B (0.63 ± 0.15 vs 0.66 ± 0.10; $P = .36$). At 4 weeks of follow-up, ABI was significantly increased in group A (1.05 ± 0.15; $P = .0004$) but remained unchanged in group B (0.62 ± 0.1). WBC counts of the two groups were comparable at baseline (group A: 7.6 ± 2.26 × 10^6/mL and group B: 7.8 ± 2.02 × 10^6/mL, $P = .81$). In group A, the leukocyte count significantly decreased after angioplasty from 7.6 ± 2.26 to 6.89 ± 1.35 × 10^6/mL ($P = .03$). For group B, WBC count did not differ significantly compared with baseline (7.76 ± 2.64 × 10^6/mL; $P = .94$). No effects were observed on hs-CRP or fibrinogen from endovascular therapy.**

Conclusion: **Endovascular revascularization with reestablishment of peripheral arterial perfusion improves FMD and reduces WBC count in patients with claudication. Revascularization may therefore have clinical implications beyond relief of symptoms, for example, reducing oxidative stress caused by repeated muscle ischemia or increased shear stress due to improved ambulatory activity. (J Vasc Surg 2008;48:1211-6.)**

Peripheral arterial obstructive disease (PAOD) is a common manifestation of atherosclerosis affecting >5% of the aged population.[1] Despite the low rate of peripheral complications and amputation, PAOD is associated with a minimal to severe impairment in functional activity and with an increased risk of future cardiovascular events.[2-5] For this reason, PAOD is considered a marker for systemic atherosclerosis. To date the most powerful prognostic indicator in PAOD patients is the ankle-brachial pressure index (ABI).[6]

Recent data suggest that increased inflammatory activity and endothelial dysfunction could be linked in PAOD patients and affect cardiovascular outcomes.[7,8] The degree of elevation of white blood cell (WBC) count within the normal range is a marker for increased risk for cardiovascular events in patients with PAOD.[9,10] This had been attributed to repeated muscle ischemia producing oxidative stress, with subsequent subclinical inflammatory activation.[7,11-13] For example, treadmill exercise in these patients is associated with a systemic inflammatory response[14,15] and acute systemic endothelial dysfunction at distant sites.[12] Thus, the ischemia–reperfusion injury associated with intermittent claudication could be among the causes for increased inflammatory activity and endothelial dysfunction in PAOD patients.[12,16,17]

Claudication also results in decreased physical activity and hence reduced shear stress.[16] Repeated shear stress has been shown to be one of the strongest stimuli for improvement of endothelial function through an increase in nitric oxide synthesis.[17,18] The two factors, postischemic muscle reperfusion and decreased shear stress, seem to be synergistic causes for deterioration of endothelial function in PAOD patients.

In recent years noninvasive ultrasound-based assessment of brachial arterial flow-mediated dilatation

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(FMD) has been used to study this specific vascular impairment (endothelial dysfunction) consisting in a decreased ability of the artery to dilated upon augmented blood flow after a transient forearm ischemia.[19] Impaired FMD is thought to be linked to nitric oxide availability in the endothelium.[20] In addition, a predictive value of FMD for cardiovascular events in patients with PAOD has been reported recently.[8,21]

The aim of this study was to prospectively assess whether the correction of intermittent leg ischemia by endovascular revascularization is associated with a reduction in inflammatory mediators and thus an improvement in endothelial function.

METHODS

Study design. The study was conducted at a tertiary referral center as a prospective, open, randomized, controlled, single-center follow-up evaluation assessing the effect of lower limb endovascular revascularization on endothelial dysfunction and inflammatory indicators (plasmatic procoagulant activity) in patients with symptomatic PAOD. Only patients with chronic and stable PAOD (Rutherford class 2 to 3) due to femoropopliteal obstruction were eligible for the study.[22] Exclusion criteria were history of lower limb or coronary revascularization, acute ischemic event within the last 3 months, chronic inflammatory disorders, moderate or severe renal insufficiency, and severe liver disease. Patients with incompressible tibial arteries and persistent claudication after angioplasty were not eligible for the study.

Randomization for angioplasty (group A) or conservative treatment (group B) was accomplished by a procedure that used a random numeric sequence. The investigators who performed FMD and laboratory analyses were blinded to patient treatment allocation. The local ethic committee approved the study, and all patients gave written informed consent.

Assessment of brachial artery FMD, WBC count, high-sensitive C-reactive protein (hs-CRP), and fibrinogen were performed at baseline and at 4 weeks after randomization in both groups. Before the investigations, patients were at rest overnight and were not allowed to consume nicotine, caffeine, or to take vasoactive drugs for at least 10 hours before the experiments and blood sampling. Patients were not exposed to any other study drug or therapeutic treatment.

Endovascular procedures. Assessment before and after the intervention included clinical examination, Doppler measurements of lower limb occlusive pressures with calculation of the ankle-brachial index (ABI), color duplex sonography, and determination of routine laboratory tests.

Endovascular treatment was performed in the routine manner. A 4F to 6F sheath that was compatible with an over the wire low-profile dilation balloon and, occasionally, an additional stenting system, which was at the discretion of the interventionalist, was introduced antegrade into the common femoral artery of the affected leg. After sheath placement and diagnostic angiography, 5000 U of unfractionated heparin was injected intra-arterially.

Postinterventional therapy lasted 4 weeks and consisted of aspirin (100 mg/d) or clopidogrel (75 mg/d), or both in case of stent insertion. To exclude any medication effects on the investigated indicators, medication remained unchanged except for clopidogrel in case of stent implantation (2 patients). This medication was initiated after baseline assessment and angioplasty with stent implantation and lasted for 28 days.

Follow-up visits were done at day 30 to 32 after the intervention. Successful angioplasty was defined by a final angiogram with residual stenosis of $<30\%$ and postinterventional ABI improvement of at least 0.1. In addition, pain free walking distance was proven the day after the procedure and at 30 to 32 days later by treadmill testing.

Assessment of FMD. Ultrasound assessment of endothelial-dependent FMD of the brachial artery was done according to recently reported guidelines.[23] The study was performed between 8 and 10 AM in a temperature-controlled room (20° to 22°C) with subjects resting in a supine position. Brachial diameter was imaged using a high-resolution (14-MHz line array) transducer ultrasound system (Siemens, Erlangen, Germany) equipped with electronic callipers, vascular software for two-dimensional imaging, color and spectral Doppler, and internal electrocardiogram.

The brachial artery was imaged at a location 2 to 5 cm above the cubital fossa. A sphygmomanometer cuff was placed on the forearm. The cuff was inflated at least 50 mm Hg above systolic pressure to occlude artery inflow for 5 minutes. All vasodilation measurements were made at the end of diastole. Off-line measurements were performed on a personal computer using the brachial reactivity analysis software (Siemens). The response of the vessel diameter to reactive hyperemia was calculated and expressed as a percentage change relative to the diameter immediately before cuff inflation. Off-line analysis was performed by one operator (A. S.) in a blinded fashion.

Assessment of ABI and treadmill testing. The ABI was calculated with the patient supine. The highest systolic pressure of the anterior or posterior tibial artery was measured in each limb and was divided by the highest brachial artery pressure. Standardized treadmill testing was performed at 3.2 km/h and 12% inclination, 1 day postprocedure and 4 days later, to assess 10 minutes of pain-free walking time in patients after angioplasty.

Biochemistry. Measurement of hs-CRP was done using an immunoturbidimetric detection method (Roche, Hitachi Modular P800, Basel, Switzerland). Fibrinogen clotting was measured according to the Clauss method on a Behring BCS coagulation analyzer using Multifibren U (Dade Behring Diagnostics, Siemens Healthcare Diagnostics, Deerfield, Ill).[24] Platelet and WBC counts were measured by an LH-750 and LH-780 System (Beckman-Coulter Inc, Fullerton, Calif) and ADVIA 120 Hematology system (Siemens Healthcare Diagnostics). Enzymatic methods were used to measure plasma total cholesterol and triglycerides (Roche). Low-density lipoprotein cholesterol was calculated using the Friedewald formula.[25]

Table I. Clinical characteristics of patients with peripheral arterial obstructive disease in group A (angioplasty) and group B (conservative treatment)

Variable	*Group A (n = 17)*	*Group B (n = 16)*	P
Age, mean (range), years	66 (47-82)	72 (53-84)	.25
Sex, No.			
Males	11	6	.12
Females	6	10	
Body mass index, kg/m^2	26.2	26.8	.69
Hypertension, No. %	12 (71)	12 (75)	.54
Diabetes mellitus, No. %	4 (24)	4 (25)	.73
Dyslipidemia, No. %	9 (56)	11 (68)	.10
Smoking, No. %			
Active	8 (47)	8 (50)	
Former	3 (18)	7 (44)	.08
Never	6 (35)	1 (6)	
Coronary artery disease, No. %	4 (23)	4 (25)	.73
Cerebrovascular disease, No. %	3 (17)	0 (0)	.10
Medication, No. %			
Aspirin/clopidogrel	16 (94)	14 (87)	.90
Oral anticoagulation	1 (6)	3 (13)	.76
Statin	7 (41)	9 (56)	.17
ACE inhibitor	7 (41)	6 (38)	.89
Calcium antagonist	2 (11)	1 (6)	.67
Angiotensin receptor blocker	3 (17)	4 (25)	.45

ACE, Angiotensin-converting enzyme.

Statistical analysis. Data are expressed as mean ± standard deviation (SD). Data were analyzed using the Mann-Whitney *U* test for intergroup comparison and the Wilcoxon signed rank test for intragroup comparison. Sample size calculation was based on data by Brendle et al,[26] who demonstrated an improvement of FMD by 61% (from 0.18 ± 0.03 to 0.29 ± 0.04 mm) after a 6-month walking exercise therapy. Assuming an effect size of 1.61 ($\alpha = 0.05$; power = 0.80, two-tailed) we calculated a sample size of 16 subjects per group. Expecting a drop-out rate of 20%, we had to evaluate 42 patients (21 per group). Data were analyzed with StatView 5.0.1 software (Adept Scientific, Acton, Mass). A value of $P < .05$ was considered to be significant.

RESULTS

Patient demographics. Nine patients were excluded from the study, four from group A because of persistent claudication after endovascular revascularization and five in group B due to cardiovascular events before the follow-up assessment. For analysis of indicators, only patients with complete baseline and follow-up assessment were included, resulting in 17 patients (group A) with successful angioplasty and subsequently pain-free walking distance during 10 minutes on the treadmill, and 16 patients in group B with best medical treatment. Clinical baseline characteristics did not differ among PAOD patients of both groups (Table I). Patients in whom endovascular therapy was not successful were not included.

Flow-mediated dilation. FMD did not differ significantly between group A (4.96% ± 1.86%) and B (4.60% ± 2.95%) at baseline ($P = .65$). After successful endovascular revascularization, FMD significantly increased in group A compared with baseline (6.44% ± 2.88%; $P = .02$; Fig 1). FMD of group B did not change during follow-up (4.53% ± 3.17%; $P = .92$) and differed from postinterventional FMD of group A, although this difference did not reach statistical significance ($P = .09$). The ABI was similar for group A and B at baseline (0.63 ± 0.15 vs 0.66 ± 0.10; $P = .36$). The ABI significantly increased in group A after revascularization (1.05 ± 0.15; $P = .0004$) but remained unchanged in group B at follow-up (0.62 ± 0.1; $P = .82$).

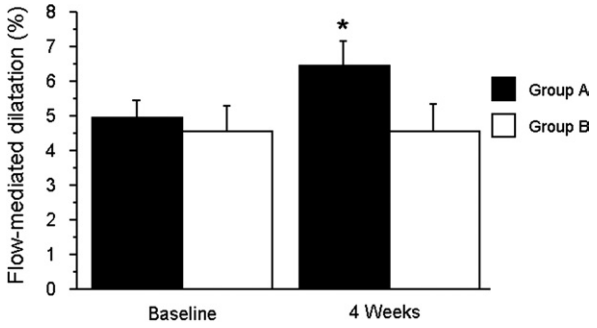

Fig 1. Endovascular revascularization in group A (*black bars*) improved flow-mediated dilation compared with baseline (*P = .02) and with group B (conservative treatment, *white bars*) at follow-up ($P = .09$). Conservative treatment did not alter flow-mediated dilation in group B ($P = .92$). *Error bars* show the standard deviation.

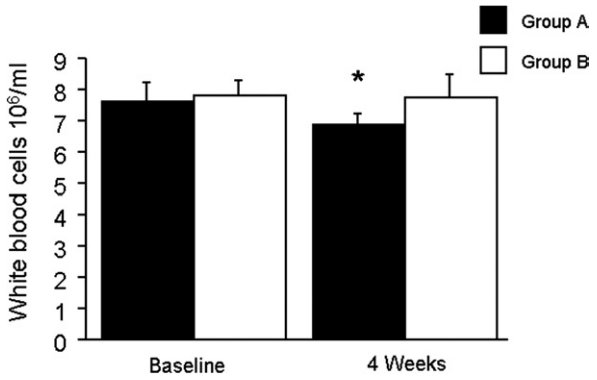

Fig 2. Effect of angioplasty on white blood cell count on group A (revascularization, *black bars*) and group B (conservative treatment, *white bars*). *Error bars* show the standard deviation. *P = .03 for group A compared with baseline.

Laboratory analysis. The WBC counts of the two groups were comparable at baseline, at 7.6 ± 2.26 × 10^6/mL for group A and 7.8 ± 2.02 × 10^6/mL for group B ($P = .81$; Fig 2). After angioplasty, a slight but significant decrease occurred in the WBC count for group A (6.89 ± 1.35 × 10^6/mL, $P = .03$). For group B, WBC count did not change significantly compared with baseline (7.76 ± 2.64 × 10^6/mL, $P = .94$). In contrast, there was no

Table II. Effect of angioplasty (group A) and conservative treatment (group B) on high-sensitive C-reactive protein and fibrinogen in patients with stable symptomatic peripheral atherosclerotic disease

Indicator	*Group A (n = 17)*	P[a]	*Group B (n = 16)*
Fibrinogen (g/L)			
Baseline	3.87 ± 0.53	.48	4.24 ± 0.69
Follow-up	3.54 ± 0.54	.52	4.0 ± 0.78
P[b]	.44		.41
Hs-CRP (mg/L)			
Baseline	2.93 ± 2.16	.46	2.67 ± 1.12
Follow-up	2.39 ± 1.46	.25	2.2 ± 1.01
P[b]	.17		.28

Hs-CRP, High-sensitive C-reactive protein.
[a]Intergroup comparison.
[b]Intragroup comparison.

relevant change of platelet count from baseline (group A, 263 ± 79 × 10^3/mL; group B, 225 ± 85 × 10^3/mL) to follow-up (group A, 260 ± 85 × 10^3/mL; group B, 212 ± 69 × 10^3/mL) or significant differences between the two groups.

Although the levels of hs-CRP and fibrinogen were slightly lower in both groups at follow-up, these differences were not significant, nor did the values differ between the groups at baseline or follow-up (Table II).

DISCUSSION

Patients with PAOD exhibit a marked deterioration of FMD and increased levels of inflammatory and oxidative stress markers, possibly due to the atherosclerotic burden, muscle ischemia and reperfusion, and decreased shear stress due to claudication.[8,13,27-29] Furthermore, higher levels of WBCs within the normal range were shown to be associated with poorer prognosis in PAOD patients.[10,30] The present study indicates that endovascular treatment of intermittent claudication ameliorates FMD and reduces WBC count.

So far, a beneficial effect has only been shown for antioxidative treatment in PAOD patients, which resulted in a transient improvement of FMD.[12,13,31] This is thought to be due to the scavenging effects of antioxidants on reactive oxygen species that result from reperfusion of ischemic muscle. Successful revascularization attenuates muscle ischemia and therefore generation of reactive oxygen species and inflammation. Inflammation and free oxygen radicals reduce nitric oxide bioavailability. The abolishment of claudication and hence generation of reactive oxygen species may partly explain our observation, because FMD has been shown to closely correlate with nitric oxide bioavailability.[20]

In addition, the limitation of physical activity by intermittent claudication is relieved through successful endovascular repair. Physical activity (ie, walking) has been shown to be the main stimulus for endothelial-dependent vasodilatation through a rise in shear stress.[32,33] An increase in endothelial nitric oxide synthesis is an important physiologic adaptation to regular exercise. Moreover, regular exercise has been shown to improve vascular function in adults independent of changes in other risk factors.[34,35] Therefore, besides being of pathophysiologic interest, our findings may also have a clinical application in that the indication for endovascular treatment in patients with intermittent claudication may be expanded beyond simple pain relief.

Epidemiologic studies have demonstrated a high prevalence of vascular events in patients with PAOD.[3,36] Several studies have clearly shown the importance of engaging in regular exercise to attenuate or reverse the disease process in patients with cardiovascular disease.[37] Continuous walking, either three times for 60 minutes or six times for 30 minutes per week, had been proposed as being sufficient for attenuation of atherosclerotic disease progression.[38] It is highly unlikely, however, that patients with PAOD and at Rutherford stages 2 or 3 are able to walk for half an hour. Studies on walking exercise in patients with PAOD demonstrate an increase of up to 400% in pain-free walking distance.[39] This increase may still be far beyond the capacity to continuously walk for half an hour to provide a sufficient stimulus for prolonged shear stress for sufficient effect on nitric oxide synthesis.

In our study, endovascular therapy resulted in an increase of walking capacity that was proven by treadmill testing 4 weeks after the procedure. Increased physical activity, although not quantified in our study, could explain the changes found already after a 4-week follow-up. It is well known that exercise training improves ambulatory function collateralization, resulting in an improved pain-free walking distance. The development of collateralization is slow, however, whereas in contrast, successful angioplasty reestablishes full walking capacity immediately. This facilitates physical activity.

Presently, it remains unclear whether the abolishment of claudication and hence reduction in oxidative stress or already increased physical activity explains a better FMD in our study population. Provided the absence of additional oxidative stress (ie, repeated muscle ischemia), it has been shown that exercise affects FMD already after a short training time of 4 weeks.[40]

Other possible factors, such as vitamin supplementation or other medications with aspirin/clopidogrel, or both, on FMD and WBC count are unlikely to have affected the present findings because patients were asked to continue their medication unchanged and to withhold any supplementation. In two patients who had stent implantation, clopidogrel medication was ceased 2 to 4 days before the follow-up assessment.

Findings of a reduced WBC count in our study may be related to the abolishment of muscle ischemia after successful revascularization. This is an important finding, because the degree of elevation of WBC count within the normal range is a marker for an increased risk of cardiovascular events.[10] In contrast, we did not find any changes in the platelet count. Similarly, hs-CRP and fibrinogen remained

unchanged in both groups, although an effect on hs-CRP due to reduction of inflammation might be expected. In accordance with our findings of unchanged hs-CRP and fibrinogen, Wahlgren et al[41] reported a transient increase in fibrinogen and hs-CRP levels within the first day after the endovascular procedure, but these markers did not differ from baseline values at the 1-month follow-up. The time period in our study may have been too short, or the study population too small, to reveal any beneficial effects of increased physical activity or decreased oxidative stress, or both, on hs-CRP and fibrinogen.

The lack of assessment of physical activity or markers of oxidative stress is a shortcoming of the present study. Future studies are needed to address these questions, both in terms of pathophysiologic understanding and therapeutic management of PAOD patients. Another limitation is the lack of structured exercise training for both groups. However, the extent of exercise training would then differ with regard to absolute walking capacity between the two groups, whereas the present scenario represents the real-world setting. Nevertheless, the possible spontaneous increase in physical activity, which is mainly attributable to relief of symptoms in the angioplasty group, demonstrates the importance of endovascular revascularization in terms of freedom from pain that might be able to counteract a sedentary lifestyle.

So far, the endovascular treatment for Rutherford stages 2 to 3 was aimed to improve patients' quality of life. If PAOD is recognized as a restriction of physical activity in a growing elderly population and endovascular or surgical revascularization can be confirmed to increase physical activity, thereby reducing cardiovascular morbidity and mortality, additional systemic benefits of revascularization in terms of public health economy may outweigh the initial costs. Future randomized studies comparing conservative vs endovascular therapy are warranted to confirm the present findings in larger patient settings incorporating cardiovascular end points.

In conclusion, endovascular revascularization for stable claudication resulting in alleviation of symptoms improves brachial artery endothelial function and decreases leukocyte count.

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AUTHOR CONTRIBUTIONS

Conception and design: MH, AS, JD
Analysis and interpretation: MH, JD, CK, ND, IB, AS
Data collection: MH, JD, AS
Writing the article: MH, JD, AS
Critical revision of the article: ND, IB, CK
Final approval of the article: MH, JD, CK, ND, IB, AS
Statistical analysis: MH, AS
Obtained funding: MH, JD, AS
Overall responsibility: MH
MH and JD contributed equally to this work

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